

Docket No.: 2815-0347PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Brian FROSTRUP et al.

Application No.: 10/566,384

Confirmation No.: 5532

Filed: January 30, 2006

Art Unit: 1626

For: 2-METHOXYMETHYL-3-(3,4-
DICHLOROPHENYL)-8-
AZABICYCLO[3.2.1]OCTANE TARTRATE
SALTS

Examiner: V. Rodriguez-Garcia

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

As required under § 41.37(a), this brief is filed within two months of the Notice of Appeal filed in this case on June 1, 2009, with the due date having been extended by one (1) month, and is in furtherance of the Notice of Appeal.

The fees required under § 41.20(b)(2) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1206:

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I. REAL PARTY IN INTEREST

The real party in interest of the claimed subject matter of the above-captioned application is assignee of record, NEUROSEARCH A/S, 93 PEDERSTRUPVEJ, BALLERUP, DENMARK, as evidenced by the assignment recorded on January 30, 2006 at reel/frame 017513/0898.

II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

There are no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

Claims 13-23 are pending in the application. Claims 16-19 and 21-23 have been withdrawn from consideration by the Examiner. Claims 13-15 and 20 stand rejected and the rejection of claims 13-15 and 20 is appealed. Claims 1-12 have been cancelled.

IV. STATUS OF AMENDMENTS

No amendments to the claims were submitted in response to the Office Action issued on December 1, 2008. All previously submitted amendments have been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The instant invention is drawn to a salt selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate (claim 13), as disclosed on page 1, lines 1-3 of the specification.

Claim 14 is specifically drawn to the L-tartrate salt and is supported by page 1, lines 1-2 of the specification.

Claim 15 is specifically drawn to L-tartrate monohydrate and is supported by page 1, lines 1-2 of the specification.

Finally the instant invention is drawn to a pharmaceutical composition, comprising a therapeutically effective amount of a salt of a salt selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate, together with at least one pharmaceutically acceptable carrier, excipient or diluent (claim 20), as disclosed on page 1, lines 14-16 of the specification..

VI. GROUNDS OF OBJECTION TO BE REVIEWED ON APPEAL

Whether claims 13-15 and 20 are unpatentable under 35 U.S.C.§103 for being obvious over Scheel-Kruger et al., U.S. Patent No. 6,288,079 B1, combined with Berge et al., “*Pharmaceutical Salts*,” J. Pharm. Sci., Vol. 66(1), pp. 1-19, (1977).

(VII) ARGUMENT.

Instant claim 13 is directed to a salt selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate. Claims 14 and 15 further define the compound of the invention as specifically being the L-tartrate salt or L-tartrate monohydrate form of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate, respectively.

In the Office Action of July 10, 2008, the Examiner rejected Claims 13-15 and 20 under 35 U.S.C. 103(a) as being unpatentable over Scheel-Kruger et al. (US 6,288,079B1) as evidenced by Berge et al. (J. Pharm. Sci. 1977; 66(1); 1-19). Scheel-Kruger et al. was relied upon for disclosing the salt (1 R, 2R, 3S, 5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane citrate (column 22, lines 5-40, example 15). The reference was further relied upon for disclosing pharmaceutically acceptable addition salts, including tartrate salts; that these salts are formed by procedures well known in the art (column 5, lines 24-30) and that the compounds may exist in either anhydrous or solvated forms (monohydrate, polyhydrate) (column 6, lines 11-15), and as isomers and mixtures (column 6, lines 16-20).

Berge et al. was relied upon for teaching that tartrate salts are the 4th most commonly commercially marketed pharmaceutical salts (page 2, Table 1). The Examiner asserted that Berge et al. further teaches that organic salts of basic drugs, such as tartrate salts, are more soluble in water than inorganic salts and that dicarboxylate salts with small alkyl groups where the alkyl group is hydroxylated, increases the solubility of the drug (page 8, 1st column, 1st and 2nd paragraph).

In supporting the rejection, the Examiner relied upon the holding in *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007). cf. *In re Aller*, 220 F.2d 454 (CCPA 1955), which states, "It is a matter of routine optimization for a person of skill in the art to determine the best pharmaceutically acceptable salt from those salts known to be useful in pharmaceutical active agents."

The Examiner, concluded, that "it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to make the salt (1 R, 2R, 3S, 5S)-2-

methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate, the L-isomer of such octane tartrate salt, the monohydrate of such octane L-tartrate salt and a pharmaceutical composition comprising a therapeutically effective amount of a salt of (1R, 2R, 3S, 5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate, as per the teachings of Scheel-Kruger et al.” (See page 5, liens 7-14 of the July 10, 2008 Office Action.)

In response to the rejection, Appellants submitted a Declaration under 37 C.F.R. §1.132, of Dr. Brian Frøstrup, on November 10, 2008, a copy of which is attached hereto. The Declaration of Dr. Frøstrup provided evidence that when compared to the citrate salt of Scheel-Kruger et al., the salt of the present invention shows an unexpected and substantial improvement in hygroscopic properties.

Specially, the DSV sorption profile for the citrate salt of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane shows the citrate salt to be hygroscopic. The Declaration of Dr. Frøstrup explains that the mass increase at ambient relative humidity indicates the formation of a monohydrate. Additionally, when comparing the present invention (i.e. the tartrate salt) to the citrate salt, for cycle 1, there was a near 20% improvement in mass change at high relative humidity. At decreasing humidity there was still a baseline improvement of 5% change in mass. The Declaration also shows that there was nearly a 15% improvement in mass change for cycle 2 at high relative humidity and the same baseline improvement of 5% change in mass.

The non-hygroscopic nature of the tartrate salt is important for any commercial use. Scheel-Kruger et al. do not teach or suggest that the tartrate salt would possess any such special properties. The data provided shows that the unexpected substantial improvement in hygroscopic properties of the tartrate salt is an unexpected advantageous result.

The specific compounds of claims 13-15 and 20 are neither derived from nor suggested by Scheel-Kruger et al. combined with Berge et al. Nor is there any motivation to modify Scheel-Kruger et al. to achieve the invention. Due the unpredictability in the chemical arts and the particularly unique structure of the claimed compound, the present invention is not obvious in light of Scheel-Kruger et al. and Berge et al. and the Examiner is applying hindsight reconstruction to achieve the invention.

There is no motivation or reason that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) into a particular salt form, since the Scheel-Kruger et al. and Berge et al. do not disclose, teach or suggest that the tartrate salt would possess any such special properties, especially the non-hygroscopic property of the tartrate salt which is important for any commercial use. Indeed, the data provided within the submitted Declaration shows that the non-hygroscopic nature of the instantly claimed compounds is a substantial unexpected improvement in hygroscopic properties of the instantly claimed tartrate salt.

Since Scheel-Kruger et al. and Berge et al. do not disclose or suggest the unexpected advantageous non-hygroscopic properties of the tartrate salt of the instant claims, a chemist would not be motivated to modify the compounds of Scheel-Kruger et al. via Berge et al. to make the present invention.

In response to the above arguments, the Examiner asserted in the Office Action of December 1, 2008, that the Declaration Dr. Brian Frøstrup was insufficient to overcome the rejection. See pages 2-4 of the Office Action of December 1, 2008. The Examiner suggested that a skilled artisan in the chemical or pharmaceutical arts would have envisioned to make the tartrate salt of the claimed compound from Scheel-Kruger et al. with expectation of reasonable success, because there are only a finite number of pharmaceutically acceptable salts disclosed in Scheel-Kruger et al. and the tartrate salts are also the 4th most commonly commercially marketed salts approved by the FDA as seen in Berge et al.

The Examiner's finding of insufficiency of the data within the Declaration was based largely on the Examiner's reliance on the precedence of *Pfizer, Inc. v. Apotex, Inc.*, 82 USPQ 2d. 1321 (Fed. Cir. 2007).

The Examiner in the Office Action of December 1, 2008 again asserted that Scheel-Kruger et al. (column 5, lines 24-34 and column 22, lines 5-44) discusses salts of the active compounds, including tartrate salts, and specifically the compound (1R, 2R, 3S, 5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane. As noted above, the Examiner relied on Berge et al. for the general knowledge that tartrate salts are commonly (4th most common) used in the pharmaceutical arts. Finally, the Examiner further asserted that due

to the common use of tartrate salts (based on Berge et al.), a skilled artisan in the pharmaceutical art would have envisioned making the tartrate salt of the claimed compound from Scheel-Kruger et al. with an expectation of reasonable success.

Appellants respectfully disagree with the Examiner that the Declaration of Dr. Frøstrup does not show unexpected results. An Information Disclosure Statement filed January 30, 2006, the article of Keverline-Frantz *et al.*, “*Synthesis and ligand binding of tropane ring analogues of paroxetine*,” *J. Med. Chem.*, Vol. 41, No.2, pp 247-297 (1998) (hereinafter “Keverline”). A copy of this article is attached hereto.

Keverline is directed to tropane compounds, *i.e.*, compounds structurally related to the compounds of the present invention. Keverline discloses the synthesis of fifteen compounds, which are tartrate salts (see Keverline, pages 253-256). Within the descriptions for the compounds, 11/15 are tartrate salts of tropanes that are characterized as “hygroscopic.” The tropane tartrate salt compounds characterized as being “hygroscopic” in Keverline include:

(1R)-3 α -(4-Fluorophenyl)-2 β -(hydroxymethyl)tropane
3 β -(4-Fluorophenyl)-2 α -[[3,4-(methylenedioxy)phenoxy]methyl] tropane
3 α -(4-Fluorophenyl)-2 β -[[3,4-(methylenedioxy)phenoxy]methyl] tropane
(1S)-3 β -(4-Fluorophenyl)-2 α -[[3,4-(methylenedioxy)phenoxy]methyl] tropane
(1S)-3 α -(4-Fluorophenyl)-2 β -[[3,4-(methylenedioxy)phenoxy]methyl] tropane
3 β -(4-Fluorophenyl)-2 β -[[3,4-(methylenedioxy)phenoxy]methyl] nortropane
(1R)-3 β -(4-Fluorophenyl)-2 α -[[3,4-(methylenedioxy)phenoxy]methyl] nortropane
(1R)-3 α -(4-Fluorophenyl)-2 β -[[3,4-(methylenedioxy)phenoxy]methyl] nortropane
(1S)-3 β -(4-Fluorophenyl)-2 β -[[3,4-(methylenedioxy)phenoxy]methyl] nortropane
(1S)-3 β -(4-Fluorophenyl)-2 α -[[3,4-(methylenedioxy)phenoxy]methyl] nortropane, and
(1S)-3 α -(4-Fluorophenyl)-2 β -[[3,4-(methylenedioxy)phenoxy]methyl] nortropane.

Keverline is silent regarding the hygroscopicity of the remaining four tropane compounds. Thus, with regard to those compounds for which the hygroscopic properties are disclosed, all are designated as being hygroscopic. Hence, Appellants submit that the non-hygroscopic nature of the instantly claimed compound is surprising and one skilled in the art would neither predict nor expect, in view of the teachings within Keverline, that the tartrate salt compounds of the present application would, in fact, be very non-hygroscopic.

While the Examiner relies on the holding of *Pfizer, Inc. v. Apotex, Inc.*, *supra*, as supporting the rejection, the facts and holding of *Sanofi-Synthelabo v. Apotex Inc.*, 89 USPQ2d

1370 (Fed. Cir. 2008) are much more directly on point to the facts of the instantly claimed invention and associated rejection. In particular, on page 1379 of the *Sanofi-Synthelabo* decision, the court stated,

...Concerning the bisulfate salt, the district court found no evidentiary support for Apotex's argument that the '596 patent taught the dextrorotatory enantiomer of PCR 4099 as the bisulfate salt. The PCR 4099 racemate is shown in the '596 patent as the hydrochloride, not the bisulfate. The district court observed that the scientific literature listed eighty acids as candidates for forming salts with basic drug compounds, fifty-three of which acids had been used in FDA-approved drugs. The experts of both parties agreed that whether a pharmaceutically suitable crystalline salt will form from a particular acid-base combination is unpredictable. The district court distinguished the facts of this case from those of Pfizer 480 F.3d 1348, where there was evidence that based on the prior art a person of ordinary skill would have narrowed the possible salts to only a few including the claimed besylate, whereas here Sanofi presented evidence that the prior art taught away from the use of sulfuric acid with an enantiomer, for strong acids could encourage re-racemization.... Sanofi-Synthelabo v. Apotex Inc., 89 USPQ2d 1370, 1379 (Fed. Cir. 2008). (emphasis added).

The Examiner asserts that the skilled artisan would envision making the tartrate salt of Scheel-Kruger et al., since there are only a finite number of acceptable salts within Scheel-Kruger et al. and a tartrate salt is the fourth most commercially marketed salts approved by the FDA. However, based on the holding provided in *Sanofi-Synthelabo* and the disclosure of Keverline the Examiner's premise is incorrect.

The two documents cited by the Examiner do not direct the skilled artisan to the tartrate salt. The teachings of the cited references do not suggest or motivate the skilled person to select the tartrate salt. In fact, based on what was known in the art regarding tartrate salts, one skilled in the art would not be led in the direction of tartrate salts. Keverline indicates that tartrate salts of tropane compounds, which are similar to the tropane compounds of the present invention are hygroscopic. Appellants have thus distinguished the facts of the present application from those of *Pfizer, Inc. v. Apotex, Inc.*, 82 USPQ 2d. 1321 (Fed. Cir. 2007). The Declaration of Dr. Frøstrup, which demonstrates that the claimed compounds are non-hygroscopic runs counter to the prior art teaching in Keverline. Keverline teaches that tartrate salts similar to the compounds in the present invention are predominantly hygroscopic. However, the Declaration of Dr.

Frøstrup demonstrates that the exact opposite proved to be true and provides evidence that the tropane compounds of the present invention are not hygroscopic.

Appellants further submit that the Examiner's premise that the skilled artisan would select a tartrate salt is also incorrect. Based on the Keverline reference, a skilled artisan would predict that for tropane compounds, a pharmaceutically suitable crystalline tartrate salt will be hygroscopic and therefore it the field of the invention is at best completely unpredictable as to whether the claimed tropane compound would be a suitable and desirable pharmaceutical compound and, in fact, the field of the invention would actually lead one skilled in the art away from the present invention. Keverline teaches away from the use of a tartrate salt since similar tropane tartrate salt compounds were shown to be hygroscopic. Additionally, the Declaration of Dr. Frøstrup is sufficient to overcome the rejection since it shows unexpected advantageous results.

In addition, in Scheel-Kruger et al., a list of pharmaceutically acceptable salts is mentioned (see the '079 patent at column 5, lines 24-33). This group amounts to 27 different salts and includes:

Hydrochloride, hydrobromide, phosphate, nitrate, perchlorate, sulphate, citrate, lactate, tartrate, maleate, fumarate, mandelate, benzoate, ascorbate, cinnamate, benzenesulfonate, methanesulfonate, stearate, succinate, glutamate, glycollate, toluene-p-sulphonate, formate, malonate, naphthalene-2-sulphonate, salicylate, and acetate.

In the above list of salts, 9 specific salts, which are underlined, cannot be found in Table I of Berge et al. Hence, in order to arrive at the invention in the present case, the skilled artisan is first pointed in the direction of the 53 anions listed in Berge et al. Additionally, when combining the teaching of Berge et al. with the teaching of Scheel-Kruger et al., this list is further expanded by including the additional 9 salts of Scheel-Kruger et al.. Finally, the skilled artisan must select the tartrate salt among these 62 salts. However, as pointed out above, the teachings of Keverline indicate tartrate compounds that are similar are unsuitably hygroscopic. For a skilled artisan, Keverline teaches away from using tartrate salts for tropane compounds.

As in *Sanofi-Synthelabo v. Apotex Inc.*, *supra*, Appellants have provided evidence by way of the Keverline reference that the prior art teaches away from the use of tartrate salts for tropane

compounds, because tartrate salts of similar tropane compound possess undesirable hygroscopic properties. The Declaration of Dr. Frøstrup that shows that the tartrate salt compounds of the present invention are non-hygroscopic, which is an unexpected result based on the prior art. As such, the submitted Declaration is sufficient to overcome the rejections alleged by the Examiner.

In the Advisory Action of April 21, 2009, the Examiner asserts that “Keverline’s tropane tartrate salts are salts of different tropane compounds, also some of them are hygroscopic and some of them are not hygroscopic.” As a first point, Appellants note that contrary to the assertion by the Examiner, none of the compounds of Keverline are indicated in the reference as being non-hygroscopic. For the disclosed tropane compounds of Keverline, 11/15 are disclosed as specifically being hygroscopic and the reference is silent as to the hygroscopic properties of the remaining four compounds. However, there is absolutely no basis to assume that the silence in the reference regarding the hygroscopic properties means that those four compounds are not hygroscopic. It is more likely that the hygroscopic properties were simply not measured.

With regard to the assertion by the Examiner that “Keverline’s tropane tartrate salts are salts of different tropane compounds”, Appellants have interpreted the Examiner’s comments to intend that the compounds in Keverline are not the same class of tropanes as the instant invention. However, the Examiner is scientifically incorrect in this position. The compounds of Keverline are closely related to the compound of the instant invention. The compound of the instant invention is a tropane having substituents in three positions, namely in the 2-position, the 3-position and in the 8-position.

In the 2-position, the substituent of the instant invention is always methoxymethyl (i.e. an alkoxyalkyl), whereas for the compounds of Keverline, the substituent is hydroxymethyl or 2,3-methylenedioxy-phenoxyethyl, which in general terms may be described as a substituted phenoxyethyl group. In the 3-position, the compound of the instant invention is substituted with 3,4-dichlorophenyl, whereas the compounds of Keverline is substituted with 4-fluorophenyl and in the 8-position, the compound of the instant invention is substituted with hydrogen, whereas the compounds of Keverline is substituted with either hydrogen or methyl.

Consequently, one skilled in the art would consider the instantly claimed invention and those of Keverline to be structurally related and within the same class of compounds.

As a second point, the Examiner notes in the Advisory Action that the only comparison was against a citrate salt and that “For a meaningful comparison the properties of other salts of the claimed compounds should be tested.” With regard to the second assertion by the Examiner, Appellants respectfully note that that this position is legally incorrect. The prior art is relied upon for teaching the citrate salt. There is absolutely no basis to require that Applicants test a compound that is further away from the claims than the prior art (i.e. a salt form other than the citrate salt). Appellants are only required to show patentability over the relied upon prior art, which the Declaration does.

Finally, the Examiner has not appropriately resolved the factors spelled out in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), including the factors of determining the scope and content of the prior art, ascertaining the differences between the prior art and the claims that are at issue and evaluating any evidence of secondary considerations. Based on the above, Appellants maintain that the above mentioned *Graham* factors actually reside in Appellants’ favor, especially ascertaining the differences between the prior art and the claims that are at issue and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). *Graham v. John Deere*, 383 U.S. at 17, 148 USPQ at 467. Additionally, since the Examiner did not resolve the *Graham* factors, the rationale the Examiner provides based on M.P.E.P. § 2143 for combining the cited references is improper. To reject a claim based on the above mentioned rationale, the Examiner must resolve the *Graham* factual inquiries. MPEP §2143.

Thus, Appellants respectfully submit that the presently claimed invention is distinct from and unobvious over Scheel-Kruger et al. combined with Berge et al.

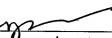
In light of the above remarks, because there is no disclosure, teaching, suggestion, reason or rationale provided in the cited references that would allow one of ordinary skill in the art to arrive at the instant invention as claimed, it follows that the same references are incapable of rendering the instant invention obvious under the provisions of 35 USC § 103(a). Based

upon the above, and applying the *Graham factors* analysis test, it is submitted that a *prima facie* case of obviousness has not been established.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: AUG 20 2009

Respectfully submitted,

By 

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Attachments: Appendices (as noted)

(VIII) CLAIMS APPENDIX

13. A salt selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate.

14. The salt of claim 13 being selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.

15. The salt of claim 13, being (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate.

20. A pharmaceutical composition, comprising a therapeutically effective amount of a salt of claim 13, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

(IX) EVIDENCE APPENDIX.

- 1) Declaration of Dr. Brian Frøstrup, submitted on November 10, 2008
- 2) Keverline-Frantz *et al.*, “*Synthesis and ligand binding of tropane ring analogues of paroxetine,*” J. Med. Chem., Vol. 41, No.2, pp 247-257 (1998)
- 3) *Sanofi-Synthelabo v. Apotex Inc.*, 89 USPQ2d 1370 (Fed. Cir. 2008)

(X) RELATED PROCEEDINGS APPENDIX

NONE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Brian FROSTRUP et al.

Application No.: 10/566,384

Confirmation No.: 5532

Filed: January 30, 2006

Art Unit: 4161

For: 2-METHOXYMETHYL-3-(3,4-
DICHLOROPHENYL)-8-
AZABICYCLO[3.2.1]OCTANE TARTRATE
SALTS

Examiner: Valerie Rodriguez-Garcia

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Brian Frøstrup, declare the following:

I am the Head of Preformulation at NeuroSearch of Ballerup, Denmark.

A copy of my curriculum vitae is attached hereto.

I have read and understand the specification and claims to the above-identified application and the outstanding Office Action of July 10, 2008 (hereinafter "Office Action").

I have also read and considered within the Office Action the 35 U.S.C. 103(a) rejection.

As to the above rejection, the Examiner cites Scheel-Kruger *et al.*, US Patent No. 6,288,079 B1 (which is the U.S. equivalent to WO 97/30997) in which the citrate salt is mentioned.

Below is data that shows that the salt of the present invention, when compared to the citrate salt of Scheel-Kruger *et al.*, shows an unexpected substantial improvement in hygroscopic properties. The non-hygroscopic nature of the tartrate salt is important for any commercial use. Scheel-Kruger *et al.* do not teach or suggest that the tartrate salt would possess any such special properties. Based on the above, as well as the data below, the unexpected substantial improvement in hygroscopic properties of the tartrate salt is an unexpected advantageous result.

The above arguments and the data explained below were presented to the International Preliminary Examining Authority (IPEA) when replying to the First Written Opinion of the ISA. Based on the above submission, the IPEA acknowledged the inventive step of the claimed invention. Enclosed is Exhibit A, which is a copy of the positive International Preliminary Report on Patentability (IPRP), for the Examiner' convenience and consideration. The IPRP discussed the data presented below.

In support of the Response to the Office Action, the following data is presented:

Hygroscopicity as measured by Dynamic Vapour Sorption (DVS)

The citrate salt and the L-tartrate salt (monohydrate) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane were tested for their water sorption characteristics as a function of increasing and decreasing humidity.

The sample weight was taken as the dry weight after equilibration at 0%RH (relative humidity). The adsorption cycles were sequentially stepped at 10% intervals from 0% to 95%RH.

The desorption cycle was the reverse of the adsorption cycle and was sequential after the adsorption cycle. A second adsorption-desorption cycle was also sequentially performed.

Citrate salt

The DSV sorption profile for the citrate salt is shown in Figure 1. The profile shows the salt to be hygroscopic. The mass increase of up to 3% at ambient relative humidity indicates the formation of a monohydrate. At high relative humidity the mass increase is 15% or more. When decreasing the relative humidity, the salt keeps about 5 % mass increase.

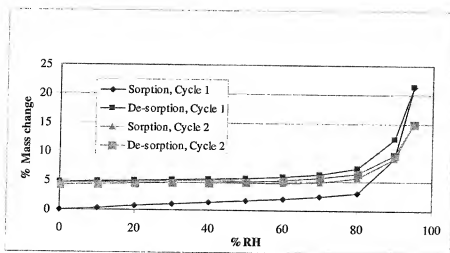


Figure 1. DSV sorption profile of the citrate salt.

Tartrate salt

The DSV sorption profile for the tartrate salt is shown in Figure 2. The profile shows the salt to be non-hygroscopic. A mass increase (up to 0.16 %) was due to adsorption on the surface of the compound.

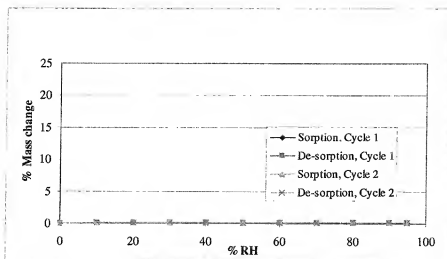


Figure 2. DSV sorption profile of the tartrate salt.

Thus, based on the above data, when compared to the citrate salt of Scheel-Kruger *et al.*, the salt of the present invention shows an unexpected substantial improvement in hygroscopic properties. As indicated in the data, the DSV sorption profile for the citrate salt (as shown in Figure 1) shows the citrate salt to be hygroscopic. The mass increase at ambient relative humidity indicates the formation of a monohydrate. When comparing the present invention to the citrate salt, for cycle 1, there is a near 20% improvement in mass change at high relative humidity. At decreasing humidity there is still a baseline improvement of 5% change in mass.

Also indicated is a near 15% improvement in mass change for cycle 2 at high relative humidity and the same baseline improvement of 5% change in mass.

As indicated, the non-hygroscopic nature of the tartrate salt is important for any commercial use. Scheel-Kruger *et al.* do not teach or suggest that the tartrate salt would possess any such special properties. The data provided shows that the unexpected substantial improvement in hygroscopic properties of the tartrate salt is an unexpected advantageous result.

STATEMENT UNDER 18 U.S.C. § 1001

I hereby declare that all statements made herein of any own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 2008-11-05

Brian Frøstrup
Brian Frøstrup

Enclosures: Exhibit A: International Preliminary Report on Patentability

NEUROSEARCH

BFR
05.11.2008

CURRICULUM VITAE

Name:	Brian Frøstrup
Born:	December 16, 1973
Graduated:	July 1999, Royal Danish School of Pharmacy
Diploma Brewmaster	March 2001, Scandinavian School of Brewing
September 1999 - March 2001	Brewmaster Trainee, Carlsberg Copenhagen
April 2001 - May 2001	Brewmaster , Carlsberg Copenhagen
June 2001 - February 2004	NeuroSearch, Research scientist, Pharmaceutical development Major field of work: Solid and solution state characterization of new chemical entities.
March 2004 -	NeuroSearch, Head of Preformulation. Major field of work: Solid and solution state characterization of new chemical entities.

Publications

Poster

Frøstrup, B., Jensen, K.S, Solid-state characterisation of *NSB L-Tartrate* Monohydrate and Anhydrous Form II and Form III. PhandTA 7. Sep 2003.

Patent publications

WO 2005/011694, filed on 29-07-2004
2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate salts
Brian Frøstrup, Frank Wätjen, Klaus Snej Jensen

WO 2006/064031, filed on 15-12-2005
Enantiomers of 3-heteroaryl-8H-8-azabicyclo (3.2.1)oct-2-ene and their use as monoamine neurotransmitter re-uptake inhibitors
Dan Peters, David Tristram Brown, Börje Egestad, Eva Dam Christoffersen, David Spencer Jones, Brian Frøstrup, Elsebet Østergaard Nielsen, Gunnar M. Olsen, John Paul Redrobe

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing
(day/month/year)

23.05.2005

Applicant's or agent's file reference
264-204-WO

IMPORTANT NOTIFICATION

International application No.
PCT/EP2004/051651

International filing date (day/month/year)
29.07.2004

Priority date (day/month/year)
31.07.2003

Applicant
NEUROSEARCH AS et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions are patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 264-204-WO	FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/EP2004/051651	International filing date (day/month/year) 29.07.2004	Priority date (day/month/year) 31.07.2003	
International Patent Classification (IPC) or national classification and IPC A61K31/46, A61P25/00, C07D451/02			
Applicant NEUROSEARCH AS et al.			
<ol style="list-style-type: none"> 1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 5 sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: <ol style="list-style-type: none"> a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows: <ul style="list-style-type: none"> <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions). 			
<ol style="list-style-type: none"> 4. This report contains indications relating to the following items: <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Box No. I Basis of the opinion <input type="checkbox"/> Box No. II Priority <input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input type="checkbox"/> Box No. VIII Certain observations on the international application 			
Date of submission of the demand 19.03.2005	Date of completion of this report 23.05.2005		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Molina de Alba, J Telephone No. +49 89 2399-7823		



Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-12 as originally filed

Claims, Numbers

1-12 received on 19.03.2005 with letter of 19.03.2005

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-12
	No: Claims	
Inventive step (IS)	Yes: Claims	1-12
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	12?

2. Citations and explanations (Rule 70.7):

see separate sheet

1) Reference is made to the following document:

41 **D1:** WO 97/30997 A (NEUROSEARCH AS ; SCHEEL KRUEGER JOERGEN (DK);
MOLDT PETER (DK); WAETJE) 28 August 1997 (1997-08-28)

2) The present application relates to (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate salts and their use as monoamine neurotransmitter re-uptake inhibitors.

3) Re Item V

3.1 Novelty (Art. 33(2) PCT)

None of the cited documents discloses the particular compound (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate. The claimed subject-matter is therefore regarded as novel.

3.2 Inventive Step (Art. 33(3) PCT)

D1 is considered to be the closest state of the art. This document relates (cf. abstract and pg. 1, par. 1) to the preparation of particular tropane derivatives and their use as monoamine neurotransmitter re-uptake inhibitors in the treatment of disorders such as Parkinson's disease, depression, obsessive compulsive disorders, panic disorders, dementia, etc. For the preparation of the medicinal compositions, **D1** suggests (cf. pg. 7, par. 1) as pharmaceutically acceptable salts a list of acid addition salts comprising tartrate. It is also mentioned (cf. pg. 8, par. 6), that the resolution of racemic mixtures may be carried out by fractional crystallization of D- or L-tartrates, mandelates, or camphorsulphonates. Example 15 of **D1** discloses the preparation of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane and its citrate salt.

The subject-matter of the application differs from **D1** in that the compound involved is a tartrate and not a citrate. The Applicant has shown by means of comparative examples (filed on 19.03.2005) that the tartrate of the invention shows much better properties as regards hygroscopicity than its homologous citrate salt. The problem to be solved by the present

application may thus be regarded as providing less hygroscopic salts of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane.

Even though **D1** mentions (see paragraphs indicated above) tartrates among the suitable pharmaceutical salts, this document is silent as to the hygroscopic properties of the resulting substances. Thus, there is no motivation in **D1** for the skilled person to particularly select tartrates among other pharmaceutically acceptable salts. As this selection is accompanied by an unexpected effect (drastically low hygroscopic character) the claimed subject-matter involves an inventive step.

3.3 Industrial applicability (Art. 33(4) PCT)

Is acknowledged for claims 1-11.

For the assessment of the present Claim 12 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States and the patentability can also be dependent upon the formulation of the claims.

Synthesis and Ligand Binding of Tropane Ring Analogues of Paroxetine

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Chemistry and Life Sciences, Research Triangle Institute, P.O. Box 12194, Research Triangle Park, North Carolina 27709, and Neuroscience Branch, National Institute on Drug Abuse (NIDA) Addiction Research Center, P.O. Box 5180, Baltimore, Maryland 21224

Received October 3, 1997

(3*S*,4*R*)-4-(4-Fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine [(3*S*,9*R*)-**3**, paroxetine] is a selective serotonin reuptake inhibitor (SSRI) used as an antidepressant in humans. In previous studies, we reported that certain (1*R*)-3*β*-(substituted phenyl)nortropine-2*β*-carboxylic acid methyl esters (**2a**) exhibited high affinity and reasonable selectivity for the serotonin transporter (5-HTT). The major structural differences between **2a** and (3*S*,4*R*)-**3** are that **2a** possesses a different absolute stereochemistry and has an ethylene bridge not present in **3**. In addition, **2a** possesses a carbomethoxy substituent adjacent to the aryl ring, whereas (3*S*,4*R*)-**3** contains a [3,4-(methylenedioxy)phenoxy]methyl group. In this study, we present the synthesis and biological evaluations of six of the possible eight isomers of 3-(4-fluorophenyl)-2-[[3,4-(methylenedioxy)phenoxy]methyl]nortropine (**4**). The data for inhibition of [³H]paroxetine binding show that (1*R*)-2*β*,3*α*-**4c**, which has the same stereochemistry as paroxetine, has the highest affinity at the 5-HTT. Strikingly, the most potent compounds for inhibition of [³H]WIN-35,428 binding were not the (1*R*)-2*β*,3*β*-isomers but rather (1*R*)-2*β*,3*α*-**4c** and (1*S*)-2*β*,3*α*-**4f**. Conformational analyses show that these isomers exist in a flattened boat conformation with pseudoequatorial substituents. Thus, the binding data show that this conformation is recognized by the DAT-associated binding site and also suggest that this conformation of paroxetine is recognized by the 5-HTT-associated binding site.

Much research has been devoted to gaining an understanding of the pharmacological action of cocaine (1).^{1,2} Considerable evidence suggests that the reinforcing or addicting properties of cocaine are due to its ability to inhibit dopamine uptake in the limbic brain area.^{3–7} Similar to dopamine, the reuptake of previously released serotonin plays the major role in regulating the synaptic availability of serotonin and thus serotonergic neurotransmission. Numerous neurochemical and behavioral outcomes are known to result from the treatment of animals with serotonin uptake inhibitors. For example, neuroendocrine, anticonvulsant, and analgesic effects, as well as changes in food intake and alcohol consumption, are observed.⁸ In addition, evidence suggests that inhibition of serotonin reuptake modulates the reinforcing properties of cocaine.^{9–13} Even though the importance of the serotonin transporter in mediating the neurochemical and behavioral actions of cocaine is now recognized, the molecular mechanism of action and regulation of this transporter are not well understood.

We, and others, have reported that certain (1*R*)-3*β*-(substituted phenyl)nortropine possessing 2*β*-carboxylic acid ester groups (**2a**)¹⁴ and 2*β*-ketone groups (**2b**)¹⁵ exhibit high potency at, and reasonable selectivity for,

the serotonin transporter relative to the dopamine and norepinephrine transporters. These compounds share structural features with the 4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine (**3**) class of serotonin uptake inhibitors. The serotonin uptake inhibitor paroxetine, which is (3*S*,4*R*)-**3**, has proven to be an effective antidepressant in humans.⁸ Both classes of compounds, **2** and **3**, contain a piperidine ring with an aryl moiety in a similar position. The major structural differences between **2a** and (3*S*,4*R*)-**3** are that (a) in **2a** the substituent *β* to the amino group is a carbomethoxy group whereas the analogous position in **3** is occupied by a [3,4-(methylenedioxy)phenoxy]methyl group, (b) the substituents in **2a** are *cis* to each other while they are in *trans* orientation in (3*S*,4*R*)-**3**, and (c) in the nortropine **2a** the positions *α* to the amino group are ethylene bridged. To gain a better understanding of the important structural features required by the nortropine class of compounds for good affinity and selectivity at serotonin transporters, we have prepared and evaluated the transporter binding properties of six of the possible eight isomers of 3-(4-fluorophenyl)-2-[[3,4-(methylenedioxy)phenoxy]methyl]nortropine (**4**).

Synthesis

Scheme 1 outlines the general synthesis used to prepare the nortropine analogues **4**. Lithium aluminum hydride reduction of the appropriate 3-(4-fluorophenyl)tropane-2-carboxylic acid methyl ester isomer **5** gives the 2-(hydroxymethyl)tropane **6**. Treatment of **6** with methanesulfonyl chloride afforded the 2-hydroxymethyl mesylate which, when heated in a tetrahydro-

¹ Research Triangle Institute.

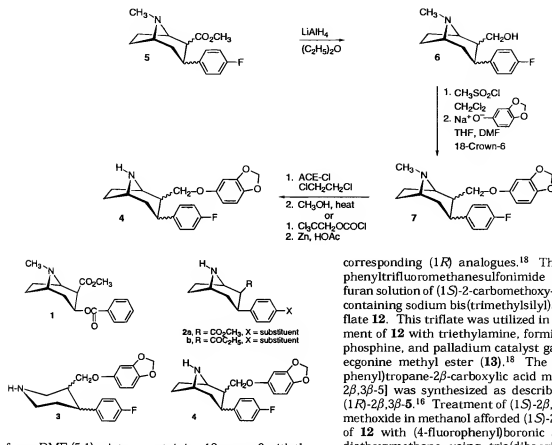
² Current address: Department of Chemistry, Delaware Valley College, 700 East Butler Ave, Doylestown, PA 18901.

³ NIDA.

⁴ Current address: Department of Pharmacology, Northeastern Ohio University, College of Medicine, 4209 State Route 44, Rootstown, OH 44272.

⁵ Current address: Yerkes Regional Primate Research Center, Emory University, 954 Gatewood NE, Atlanta, GA 30329.

Scheme 1



furan:DMF (5:1) mixture containing 18-crown-6 with the sodium salt of sesamol, yields 3-(4-fluorophenyl)-2-[[3,4-(methylenedioxy)phenoxy]methyl]tropane 7. N-Demethylation using 1-chloroethyl chloroformate (ACE-Cl) in ethylene dichloride followed by treatment with methanol, or using trichloroethyl chloroformate followed by treatment with zinc, affords the nortropane analogues 4.

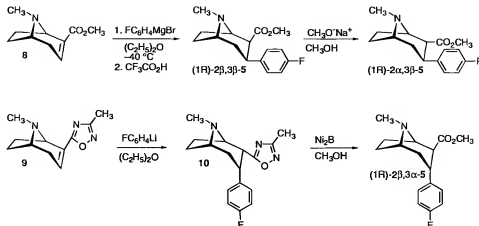
The synthesis used to prepare three of the 3-(4-fluorophenyl)tropane-2-carboxylic acid methyl esters (5) (possessing the (1*R*)-configuration) is shown in Scheme 2. The addition of (*p*-fluorophenyl)magnesium bromide to anhydroecgonine methyl ester (8), which was derived from (–)-cocaine as previously reported, gives (1*R*)-2β,3β-5. Isomerization of (1*R*)-2β,3β-5 with sodium methoxide in methanol affords (1*R*)-2α,3β-5. The addition of (*p*-fluorophenyl)lithium to the α,β-unsaturated 1,2,4-oxadiazole 9 gives the cis-addition product 10. Subjection of 10 to reduction with nickel boride in methanol results in conversion of the oxadiazole to a methyl ester and effects complete isomerization at the 2-position to give (1*R*)-2β,3β-5.¹⁷ We had hoped to prepare (1*R*)-2α,3α-5 by appropriate modification of this reductive opening of the oxadiazole ring to the 2β-methyl ester. However, all attempts to effect this conversion resulted in isomerization of the 2α group to the 2β-isomer.

Three of the (1*S*) isomers of 3-(4-fluorophenyl)tropane-2-carboxylic acid methyl esters were prepared by routes given in Scheme 3. The synthesis of 12–14, (1*S*)-2β,3α-5, and (1*S*)-2β,3β-5 is analogous to that presented in a preliminary communication for the synthesis of the

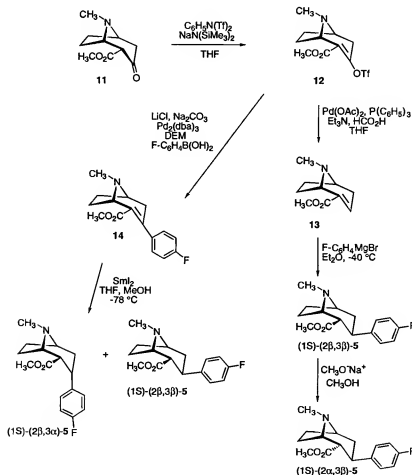
corresponding (1*R*) analogues.¹⁸ The addition of *N*-phenyltrifluoromethanesulfonimide to a tetrahydrofuran solution of (1*S*)-2-carbomethoxy-3-tropinone (11)¹⁹ containing sodium bis(trimethylsilyl)amide yielded triflate 12. This triflate was utilized in two ways. Treatment of 12 with triethylamine, formic acid, triphenylphosphine, and palladium catalyst gave (1*S*)-anhydroecgonine methyl ester (13).¹⁸ The (1*S*)-3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester [(1*S*)-2β,3β-5] was synthesized as described previously for (1*R*)-2β,3β-5.¹⁶ Treatment of (1*S*)-2β,3β-5 with sodium methoxide in methanol afforded (1*S*)-2α,3β-5. Reaction of 12 with (4-fluorophenyl)boronic acid in refluxing diethoxymethane using tris(dibenzylideneacetone)dipalladium(0) as catalyst, followed by chromatographic purification, gave the (4-fluorophenyl)tropane 14.¹⁸ Reduction of 14 with samarium (II) iodide at –78 °C using methanol as the proton source, followed by quenching with trifluoroacetic acid at 0 °C, gave a mixture of (1*S*)-3α-(4-fluorophenyl)-2β-carboxylic acid methyl ester [(1*S*)-2β,3α-5] as the major product and (1*S*)-3β-(4-fluorophenyl)-2β-carboxylic acid methyl ester [(1*S*)-2β,3β-5], which were separated by column chromatography.

Specific structural and stereochemical assignments were made for the compounds (1*R*)-7 and (1*R*)-4 using 1D ¹H and ¹³C NMR spectra and 2D COSY,^{20,21} NOESY,²² and HMQC²³ spectra. Thus, the presence of a large (10.6 Hz) coupling in the pattern of H3 in the ¹H NMR spectrum of (1*R*)-2β,3β-7a requires H3 to be axial, showing that the aryl substituent at C3 must occupy the equatorial (β) position. Similarly, the magnitude of *J*_{2,3} (5.8 Hz), which is characteristic of axial–equatorial coupling, taken together with the axial nature of H3, mandates that H2 must be equatorial, confirming the β-position of the C2 substituent. The observed NOESY interaction between H3 and H6 further confirms the axial configuration of H3 and requires that (1*R*)-2β,3β-7a be in the chair conformation. Similar arguments confirm the structural assignment of 2β,3β-4a. The observation of two large coupling constants (*J* = 12.0 Hz) for H3, which are both (COSY) associated with H2 and H4β, characterize the structure of 2α,3β-7b. The observed NOESY interactions of H2 with H4β and of H3 with H6 provide further evidence for the 2α,3β-stereochemistry and show that the compound is

Scheme 2

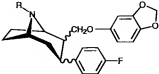


Scheme 3



in the chair conformation. The structure of the *N*-nor analogue **2α,3β-4b** is deduced from similar considerations. The compound **2β,3α-7c** also exhibits two large couplings and one smaller coupling for H3. The large couplings ($J = 10.8$ and 10.3 Hz) are associated with H2 and H4α, respectively, while the smaller coupling ($J = 8.3$ Hz) is associated with H4β. In addition, the NOESY spectrum shows an interaction between H2 and H4α. These observations cannot be reconciled with a chair conformation for this compound. Since the struc-

tures of the $\beta\beta$ isomers are definite, this isomer must possess a 3α substituent, i.e., H3 must be equatorial. However, the two large coupling constants between H3 and its geminal neighbors are inconsistent with dihedral angles of $\sim 60^\circ$, which are associated with equatorial-equatorial or equatorial-axial protons in a chair conformation. Therefore, the preferred conformation for this compound must be boatlike. This observation is supported by molecular modeling where the global energy minimum conformation was found to be a

Table 1. Comparison of Transporter Binding Potencies of the Isomers of **4** and **7**


compd	stereochemistry			IC ₅₀ (nM) ^a				
	R	2	3	5-HT [³ H]Paroxetine	DA [³ H]WIN 35,428	NE [³ H]Nisoxetine	DA/5-HT ratio ^b	NE/5-HT ratio ^b
paroxetine				0.28 ± 0.02	623 ± 25	535 ± 15	2230	1910
(1 <i>R</i>)- 7a	CH ₃	β	β	294 ± 18	308 ± 20	5300 ± 450	1.0	18
(1 <i>R</i>)- 4a	H	β	β	480 ± 21	835 ± 90	37400 ± 1400	1.7	78
(1 <i>R</i>)- 7b	CH ₃	α	β	52.9 ± 3.6	172 ± 8.8	26600 ± 1200	3.3	500
(1 <i>R</i>)- 4b	H	α	β	90 ± 3.4	142 ± 13	2500 ± 250	1.6	28
(1 <i>R</i>)- 7c	CH ₃	β	α	422 ± 16	3.01 ± 0.2	123 ± 9.5	0.007	0.29
(1 <i>R</i>)- 4c	H	β	α	5.62 ± 0.2	3.86 ± 0.2	14.4 ± 1.3	0.7	2.6
(1 <i>S</i>)- 7d	CH ₃	β	α	88.1 ± 2.8	1050 ± 45	27600 ± 1100	12	310
(1 <i>S</i>)- 4d	H	β	β	424 ± 15	1210 ± 33	17300 ± 1800	2.9	41
(1 <i>S</i>)- 7e	CH ₃	α	β	447 ± 47	1500 ± 74	2.916 ± 1950	32	640
(1 <i>S</i>)- 4e	H	α	β	55.8 ± 5.73	27.6 ± 2.4	1690 ± 150	0.49	30
(1 <i>S</i>)- 7f	CH ₃	β	α	178 ± 13	298 ± 17	12400 ± 720	1.7	70
(1 <i>S</i>)- 4f	H	β	α	19 ± 1.8	407 ± 33	1990 ± 176	21	100

^a Data are mean ± standard error of three or four experiments with triplicate values at each concentration. ^b DA/5-HT and NE/5-HT are ratios of IC₅₀ values.

flattened boat. This conformation is preferred over the lowest energy chair conformation by > 3 kcal/mol. The similarity of the NMR parameters of the *N*-nor analogue **2β,3α-4** indicates that it exists in a similar conformation.

Ligand Binding Studies

IC₅₀ values at the DA, NE, and 5HT transporters represent inhibition of 0.5 nM [³H]WIN 35,428, 0.5 nM [³H]nisoxetine, and 0.2 nM [³H]paroxetine binding, respectively, and were determined as previously described.²⁴ The IC₅₀ values for paroxetine, the six nortropane analogues **4**, and six *N*-methyl analogues **7** are listed in Table 1.

Discussion

Cocaine (**1**) is an inhibitor of the neuronal transport of norepinephrine (NE), dopamine (DA), and serotonin (5-HT) at roughly similar concentrations, i.e., with *K*_i's between 220 and 310 nM.²⁵ Biochemical binding studies indicate slight DA selectivity.^{26,27} In recent years, structure-activity relationship studies of cocaine analogues for binding at monoamine transporters, particularly at the dopamine transporter, have been explored,^{28–32} and some structural modifications that result in selectivity for the dopamine transporter over the norepinephrine and serotonin transporters have been reported.^{33–35} In the introduction section, we pointed out that serotonergic activity may affect the reinforcing effects of cocaine. Since the *in vitro* potency of cocaine (**1**) to inhibit serotonin reuptake is essentially identical with its potency to inhibit dopamine reuptake, some of the pharmacological properties of cocaine might be due to its inhibition of reuptake of serotonin. Even though the importance of the serotonin transporter in mediating the neurochemical and behavioral actions of

cocaine is now recognized, the biochemical mechanism of action and regulation of this transporter is not well understood.

The nortropane derivatives **4** were designed to be similar to known serotonin uptake inhibitors **3**. Both classes of compounds contain a piperidine ring with a 4-fluorophenyl group and a [3,4-(methylenedioxy)phenyl]methyl moiety in similar positions on the ring. The eight possible isomers of **4** are listed in Figure 1. The major structural difference between **3** and **4** is the presence of an ethylene bridge, not present in **3**, which leads to reduced conformational heterogeneity. For example, whereas the piperidine ring in the (3*S*,4*R*)-isomer of **3**, which is paroxetine, may interconvert between the chair conformations C_{3a} and C_{3e}, and the boat conformation B_{3e} and B_{3a}, the piperidine ring in the analogous isomer of **4** can only interconvert between the chair and boat conformations (see Figure 2) but not between two chair conformations. In the series of analogues **3**, the potency of paroxetine, i.e., the *trans*-(+)-3*S*,4*R* isomer, exceeds that of the other isomers by factors of 60–160.³⁶ This isomer may exist in either a diequatorial (C_{3e}) or a diaxial (C_{3a}) chair conformation, as well as in boat conformations B_{3a} and B_{3e}, all of which are interconvertible. The chair conformations C_{3a} and C_{3e} are mimicked by the isomers (1*R*)-**2β,3α-4c** and (1*S*)-**2α,3β-4e**, respectively, each of which can adopt a boat conformation, but which are not interconvertible. Therefore, it would be expected that, if conformation C_{3e} were responsible for the high potency of paroxetine, (1*S*)-**2α,3β-4e** would possess high potency to inhibit [³H]-paroxetine binding. Conversely, if conformation C_{3a} were the potent form of paroxetine, (1*R*)-**2β,3α-4c** would exhibit high potency. However, since the chair conformation of (1*R*)-**2β,3α-4c** possesses two axial substituents, the chair may not be the energy minimum conformation for this compound. Thus, we had found that although the chair is the preferred conformation of allococaine, the (2*α*,3*α*)-diaxial isomer of cocaine, boat

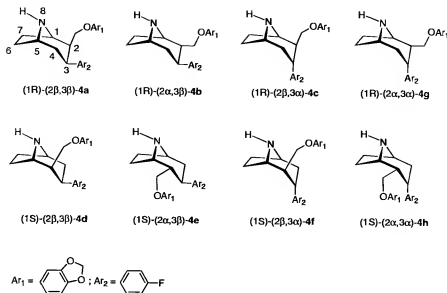


Figure 1. Isomers of 4.

conformations were preferred for diaxial analogues of 3-aryltropane-2-carboxylates.^{17,37}

Binding affinities at the 5-HT transporter, determined by inhibition of [³H]paroxetine binding (Table 1), show that the diequatorial isomers, (1*R*)-2*α*,3*β*-4*b* and (1*S*)-2*α*,3*β*-4*e*, are substantially less potent than the diaxial isomers, (1*R*)-2*β*,3*α*-4*c* and (1*S*)-2*β*,3*α*-4*f*, demonstrating that conformation C_{ee}, which may well be the low-energy conformation of paroxetine, is not well accommodated by the receptor at the 5-HT transporter. The most potent of the isomers is (1*R*)-2*β*,3*α*-4*c*, suggesting that its conformation best mimics the conformation of paroxetine which is recognized by the receptor. Since the preferred conformation of the piperidine ring of (1*R*)-2*β*,3*α*-4*c* is a substantially flattened boat, it appears that a relatively flat conformation may be required for paroxetine to bind the receptor at the 5-HT transporter. Such a conformation could resemble both the (1*R*)- and the (1*S*)-isomers of 2*β*,3*α*-4*c*, and indeed, the potency of (1*R*)-2*β*,3*α*-4*c* is only 3.4 times greater than that of the (1*S*)-isomer. The more than 1 order of magnitude lower potency of (1*R*)-2*β*,3*α*-4*c* (IC₅₀ = 5.62 nM) relative to paroxetine (IC₅₀ = 0.28 nM) may be due to steric inhibition of binding by the ethylene bridge in (1*R*)-2*β*,3*α*-4*c*.

The fact that several 3*β*-(para-substituted phenyl)-tropane-2*β*-carboxylic acid methyl esters, which possess the natural (1*R*)-cocaine stereochemistry, have high affinity at the 5-HT site³⁸ suggested that (1*R*)-2*β*,3*β*-4*a* (i.e., an analogue of the *cis* isomer of paroxetine) might also possess high affinity at the 5-HT transporter. Additionally, it had been shown that N-demethylation of 3*β*-(*p*-fluorophenyl) 2*β*-carbomethoxytropane (WIN 35,428) to give the *N*-nor analogue (RTI-142) resulted in increased affinity at the DA, 5-HT, and NE transporters.³⁹ The data in the Table indicate that these observations do not generalize to this set of compounds. In other words, N-demethylation leads to increased potency at 5-HT transporters only for the isomers which preferentially exist in a boat conformation; the effect on potency at DA and NE transporters appears to be random. In addition, it was surprising

to note that both (1*R*)-2*β*,3*β*-4*a* and (1*S*)-2*β*,3*β*-4*d* had low affinity for all three transporters. The low affinity of (1*R*)-2*β*,3*β*-4*a* and its *N*-nor analogue (1*R*)-2*β*,3*β*-4*a* at the DAT relative to the (1*R*)-2*β*,3*α*-isomers is particularly striking. Thus, since the ratio of potencies to inhibit radioligand binding at the DAT for cocaine, which has the (1*R*)-2*β*,3*β* configuration, to allococaine, which has (1*R*)-2*β*,3*α* configuration, is 59,⁴⁰ it might have been expected that the potency of the (1*R*)-2*β*,3*β*-4*a* and (1*R*)-2*β*,3*β*-4*d* would exceed that of their (1*R*)-2*β*,3*α*-isomers. Instead, the ratio is 0.01 for (1*R*)-2*β*,3*β*-4*a* to (1*R*)-2*β*,3*α*-4*c* and 0.005 for (1*R*)-2*β*,3*β*-4*d* to (1*R*)-2*β*,3*α*-4*c*. This unexpected result may be attributable to the flattened boat conformation of (1*R*)-2*β*,3*α*-4*c* and (1*R*)-2*β*,3*α*-4*e*. A less striking but similar situation had been observed for the isomeric 3-phenyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)tropanes, where the potency of the 2*β*,3*α* isomer, which exists in a boat conformation, was only slightly lower (1.48) than that of the 2*β*,3*β* isomer, which exists in a chair conformation.³⁷

Conclusions

Six of the possible eight stereoisomers of 3-(4-fluorophenyl)-2-[[3,4-(methylenedioxy)phenoxy]methyl]-nortropane (4) have been prepared as analogues of paroxetine. Ligand binding data show that (1*R*)-2*β*,3*α*-4*c*, which is one of the isomers that has the same relative stereochemistry as paroxetine, has the highest affinity for the 5-HT transporter. Since this isomer exists in a flattened boat conformation with pseudo-equatorial substituents, it appears that a flattened boat conformation of paroxetine is recognized by the binding site at the 5-HT transporter. The order of magnitude lower potency of (1*S*)-2*α*,3*β*-4*e*, which is the other isomer that has the same relative stereochemistry as paroxetine, confirms that a chair conformation with two equatorial substituents is not recognized by the 5-HT transporter-associated receptor. The good affinity of (1*R*)-2*β*,3*α*-4*c* and (1*R*)-2*β*,3*α*-4*e* at the DA transporter suggests that tropane analogues which exist in a flat-

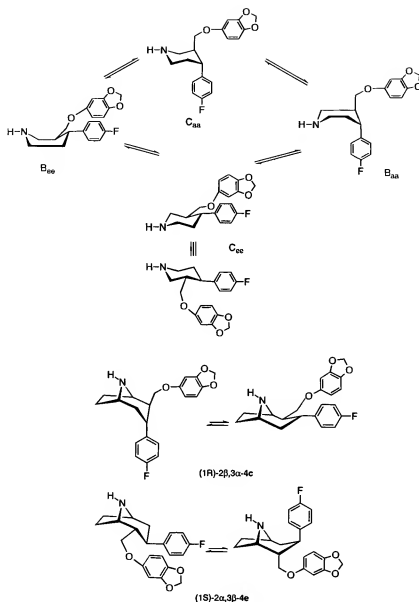


Figure 2. Chair and boat conformations.

tened boat conformation with pseudoequatorial substituents are well recognized by the DAT-associated binding site.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary tube apparatus. All optical rotations were determined at the sodium D line using a Rudolph Research Autopol III polarimeter (1 dm cell). Thin-layer chromatography was carried out on Whatman silica gel 60 TLC plates, and flash chromatography was conducted on silica gel 60 (230–400 mesh). Visualization was accomplished under UV or in an iodine chamber. Microanalyses were carried out by Atlantic Microlab, Inc. Tropinone was purchased from Lancaster Synthesis, Inc., and samarium iodide was from Fluka Chemical Corp. All other chemicals were purchased from Aldrich Chemical Co, Inc. THF and ether were freshly distilled from sodium benzophenone. All other reagents were used without further purification.

Nuclear Magnetic Resonance Studies. Routine NMR spectra were obtained on a Bruker AM-250 spectrometer. COSY, NOESY, and HMQC spectra were recorded on a Bruker

AMX-500 spectrometer operating at 500.13 MHz for ^1H using a Bruker 5 mm inverse detect broadband probe. The double quantum filtered phase sensitive COSY^{20,21} and NOESY²² were acquired as 1024 × 512 data points with a spectral width of 4800 Hz in both dimensions. The data were apodized with a squared sine function and zero filled to 2K × 2K data points prior to Fourier transformation. NOESY spectra were obtained with a 1200 ms mixing time and a recycle delay of 4 s. Heteronuclear multiple quantum correlation (HMQC)²³ spectra were acquired as 1024 × 256 data points with a spectral width of 4800 Hz in F2 and 24 375 Hz in F1. An average coupling constant of 145 Hz was used to optimize $1/2J_{\text{CH}}$ delays. The data were apodized with a squared sine function and zero filled to 2048 × 512 data points prior to Fourier transformation.

Molecular Modeling Studies. Molecular modeling was performed on a SGI O2 using Sybyl 6.3⁴¹ and Spartan.⁴² Minimum energy structures were obtained using the simulated annealing module in Sybyl. For each structure, 500 cycles were calculated with a simulated temperature of 500 K for 500 fs and then annealed to 200 K for 500 fs with an exponential ramping function. The overall boat or chair conformation was maintained during the annealing procedure by placing a

penalty function on the N-C3 torsional angle with an equilibrium value of 0° for the boat conformation and 65° for the chair conformation. The lowest energy structures for each conformation were transferred to Spartan where the structures were further optimized using MM3; then the heats of formation were obtained from semiempirical (AM1) quantum mechanics calculations.

General Synthesis of 3-(4-Fluorophenyl)-2-(hydroxymethyl)trifluoromethoxy (6). A solution of 5 (3.0 mmol) in 10 mL of Et₂O was added dropwise to a cooled slurry (0 °C) of lithium aluminum hydride (5.0 mmol) in 20 mL of anhydrous Et₂O. The reaction mixture was stirred at room temperature for 2 h and then cooled to 0 °C and quenched with NH₄Cl (~3 mL). Water was added, and the layers were separated. The aqueous layer was extracted with Et₂O. The organic layers were combined, and the solvent was removed to afford a white solid which was recrystallized from hexanes or EtOAc. Results from each isomer are described in the following experiments.

(1R)-3β-(4-Fluorophenyl)-2β-(hydroxymethyl)trifluoromethoxy (1R)-2α,3β-6f. Recrystallization from hexanes gave 0.745 g (83%) of white solid; mp 75–78 °C; [α]_D²⁰ –59.8° (c 0.5, CHCl₃); ¹H NMR (CDCl₃) δ 1.46 (m, 1H), 1.58–1.67 (m, 1H), 1.72 (s, 1H), 1.75 (s, 1H), 2.16 (m, 2H), 2.28 (s, 3H), 2.50 (m, 1H), 3.07 (m, 1H), 3.35 (m, 2H), 3.46 (m, 1H), 3.75 (m, 1H), 7.01 (m, 2H), 7.32 (m, 2H). Anal. (C₁₅H₁₂FNO) C, H, N.

(1R)-3β-(4-Fluorophenyl)-2α-(hydroxymethyl)trifluoromethoxy (1R)-2α,3β-6f. Recrystallization from EtOAc gave 0.494 g (79%) of white solid; mp 174–176 °C; [α]_D²⁰ +26.3° (c 0.62, CHCl₃); ¹H NMR (CDCl₃) δ 1.54–1.62 (m, 2H), 1.70–2.22 (m, 6H), 2.27–2.35 (m, 1H), 2.35 (s, 3H), 3.20–3.41 (m, 4H), 6.96 (m, 2H), 7.18 (m, 2H); ¹³C NMR (CDCl₃) δ 162.33 (d), 139.21, 128.77, 128.64, 115.08, 114.74, 62.41, 61.43, 48.58, 40.84, 40.59, 37.19, 25.48, 21.26. Anal. (C₁₅H₁₂FNO) C, H, N. The alcohol was converted to the *p*-tartrate salt. Recrystallization from MeOH/Et₂O gave a white hygroscopic powder; mp 89 °C (fusion); ¹H NMR (CD₃OD) δ 1.88–2.39 (m, 7H), 2.72 (m, 1H), 2.87 (s, 3H), 3.25 (dd, 1H), 3.96 (m, 1H), 4.07 (m, 1H), 7.05 (m, 2H); [α]_D²⁰ +3.5° (c 0.20, CH₃OH). Anal. (C₁₅H₁₂FNO₄) C, H, N.

(1R)-3β-(4-Fluorophenyl)-2β-(hydroxymethyl)trifluoromethoxy (1R)-2β,3α-6f. Recrystallization from hexanes gave 0.681 g (64%, two steps from oxadiazole 10) of white solid; mp 83–84 °C; ¹H NMR (CDCl₃) δ 1.43–1.56 (m, 2H), 1.74 (m, 1H), 1.84 (m, 1H), 2.01–2.13 (m, 2H), 2.23 (s, 3H), 2.46 (m, 1H), 2.95 (m, 1H), 3.24 (m, 1H), 3.64 (m, 1H), 3.83 (m, 1H), 6.96 (m, 2H), 7.24 (m, 2H); ¹³C NMR (CDCl₃) δ 163.27 (d), 142.79, 128.66, 128.54, 115.09, 114.75, 69.11, 65.21, 60.27, 49.62, 40.88, 37.82, 35.53, 26.95, 26.53; [α]_D²⁰ –41.9° (c 0.31, CHCl₃). Anal. (C₁₅H₁₂FNO) C, H, N. The product was converted to the *p*-tartrate salt. Recrystallization from (CH₃)₂CHOH/Et₂O gave a hygroscopic off-white solid; mp 79 °C (fusion); ¹H NMR (CD₃OD) δ 1.86 (m, 1H), 2.02–2.13 (m, 3H), 2.30–2.72 (m, 3H), 2.78 (s, 3H), 3.01 (m, 1H), 3.51 (m, 2H), 3.88 (m, 1H), 7.06 (m, 2H), 7.35 (m, 2H); [α]_D²⁰ –24.0° (c 0.48, CH₃OH). Anal. (C₁₅H₁₂FNO₄·0.5 H₂O) C, H, N.

(1S)-3β-(4-Fluorophenyl)-2β-(hydroxymethyl)trifluoromethoxy (1S)-2β,3β-6f. Recrystallization from hexanes gave 1.18 g (70%) of white solid; mp 77–79 °C; ¹H NMR (CDCl₃) δ 1.46 (m, 1H), 1.67–1.58 (m, 1H), 1.72 (s, 1H), 1.75 (s, 1H), 2.16 (m, 2H), 2.28 (s, 3H), 2.50 (m, 1H), 3.07 (m, 2H), 3.35 (m, 2H), 3.46 (m, 1H), 3.75 (m, 1H), 7.01 (m, 2H), 7.32 (m, 2H); ¹³C NMR (CDCl₃) δ 161.42, 138.41, 129.86, 129.73, 115.13, 114.80, 68.56, 65.21, 61.96, 45.49, 41.19, 37.32, 36.19, 26.29, 25.18. [α]_D²⁰ +58.9° (c 0.54, CHCl₃). Anal. (C₁₅H₁₂FNO) C, H, N.

(1S)-3β-(4-Fluorophenyl)-2α-(hydroxymethyl)trifluoromethoxy (1S)-2α,3β-6f. Recrystallization from EtOAc gave 0.88 g (66%) of white solid; mp 173–175 °C; ¹H NMR (CDCl₃) δ 1.54–1.62 (m, 2H), 1.70–2.22 (m, 6H), 2.27–2.35 (m, 1H), 2.36 (s, 3H), 3.20–3.41 (m, 4H), 6.96 (m, 2H), 7.18 (m, 2H); ¹³C NMR (CDCl₃) δ 161.42 (d), 139.69, 129.22, 129.09, 115.44, 115.11, 62.71, 62.15, 61.90, 49.28, 41.20, 41.00, 37.53, 25.84, 21.62; [α]_D²⁰ –24.7° (c 0.51, CHCl₃). Anal. (C₁₅H₁₂FNO) C, H, N.

(1S)-3α-(4-Fluorophenyl)-2β-(hydroxymethyl)trifluoromethoxy (1S)-2β,3α-6f. Recrystallization from Et₂O/hexanes

gave 0.540 g (72%) of white solid; mp 83–85 °C; ¹H NMR (CDCl₃) δ 1.49 (m, 2H), 1.74 (m, 2H), 2.05 (m, 2H), 2.23 (s, 3H), 2.47 (m, 1H), 2.94 (m, 2H), 3.23 (m, 2H), 3.65 (m, 1H), 3.85 (m, 1H), 6.96 (m, 2H), 7.25 (m, 2H); ¹³C NMR (CDCl₃) δ 160.99 (d), 141.98, 128.63, 128.57, 114.93, 114.77, 68.69, 64.94, 60.16, 49.88, 40.83, 38.01, 35.49, 27.07, 26.62; [α]_D²⁰ +38.6° (c 0.29, CHCl₃). Anal. (C₁₅H₁₂FNO·0.5H₂O) C, H, N.

Procedure for the General Synthesis of 3-(4-Fluorophenyl)-2-[1,3,4-(methylenedioxy)phenoxy]methyltrifluoromethoxy (7). A solution of the appropriate isomer of 6 (2.0 mmol) in 15 mL of CH₂Cl₂ was cooled to 0 °C, and methanesulfonyl chloride (2.5 mmol) was added. Et₃N (2.0 mmol) was then added dropwise. The reaction mixture was stirred at 0 °C for 0.5 h and then at room temperature. After 3 h, CH₂Cl₂ and water were added. The reaction was basified to pH 10 with NH₄OH, and the layers were separated. The aqueous layer was extracted with CH₂Cl₂. The organic layers were combined, washed with 1 N NaOH, water, NH₄Cl solution, water, and NaCl solution, and dried over Na₂SO₄. The solvent was removed to give a colorless, slightly cloudy oil which was used without further purification.

Sodium hydride (60% dispersion, 4.0 mmol) was washed twice with hexanes under nitrogen gas. Anhydrous THF (10 mL) was added, and the slurry was cooled to 0 °C. A solution of sesamol (4.0 mmol) in 10 mL of THF was added dropwise. Eventually the mixture cleared and became yellow. The alkoxide was warmed to room temperature and refluxed for 45 min. The mesylate and 18-crown-6 ether (~5 mmol) were dissolved in 10 mL of a mixture of THF and 2 mL of DMF and added dropwise over 10 min. The reaction was warmed to room temperature after the addition was complete, refluxed for 3 h, and then stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C and quenched with water. THF was removed under reduced pressure, and water and NH₄OH were added, and the aqueous layer (pH 10) was extracted with CH₂Cl₂. The organic layers were combined, washed with 1 N NaOH, water, and NaCl solution, and dried over MgSO₄. The solvent was removed to give a light yellow oil which was purified by flash chromatography on silica gel, eluting with Et₂O/Et₃N/hexanes (27:3:70).

(1R)-3β-(4-Fluorophenyl)-2β-[1,3,4-(methylenedioxy)phenoxy]methyltrifluoromethoxy (1R)-2β,3β-7a. Purification by flash chromatography gave 0.33 g (44%) of the pure product as an oil; ¹H NMR (C₆D₆) δ 1.59 (m, 1H), 1.81 (m, 2H), 2.09 (m, 2H), 2.14 (m, 1H), 2.20 (ddd, 1H, *J* = 14.3, 5.8, 5.8 Hz), 2.38 (ddd, 1H, *J* = 11.6, 1.6, 1.6 Hz), 2.40 (s, 3H), 2.98 (ddd, 1H, *J* = 11.6, 6.2 Hz), 3.01 (ddd, 1H, *J* = 6.2, 6.2, 1.6 Hz), 3.42 (ddd, 1H, *J* = 10.8, 5.8 Hz), 4.31 (ddd, 1H, *J* = 9.7, 1.8, 1.8 Hz), 5.89 (s, 2H), 6.32 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.48 (dd, 1H, *J* = 2.3 Hz), 6.66 (dd, 1H, *J* = 8.6 Hz), 6.95 (dd, 2H, *J* = 8.8, 8.8 Hz), 7.39 (dd, 2H, *J* = 8.8, 5.8 Hz); ¹³C NMR (CDCl₃) δ 163.06, 159.20, 152.75, 148.28, 143.23, 141.82, 129.45, 129.33, 115.12, 114.78, 108.57, 108.09, 101.15, 99.90, 83.74, 55.25, 50.49, 54.52, 42.89, 33.96, 31.96, 26.98, 23.78. The *p*-tartrate salt recrystallized from 2-propanol/ethyl ether yielded a white powder which had mp 97 °C (fusion); ¹H NMR (CD₃OD) δ 2.00–2.43 (m, 7H), 2.95 (s, 3H), 3.48 (m, 2H), 3.68 (m, 2H), 4.61 (m, 1H), 5.86 (s, 2H), 6.39 (dd, 1H), 6.49 (d, 1H), 6.68 (dd, 1H), 7.03 (m, 2H), 7.36 (m, 2H); [α]_D²⁰ +11.8° (c 0.27, CH₃OH). Anal. (C₂₁H₁₈FNO₄) C, H, N.

3β-(4-Fluorophenyl)-2α-[1,3,4-(methylenedioxy)phenoxy]methyltrifluoromethoxy (1R)-2α,3β-7b. Fractions were pooled to give 0.34 g (51%) of the product as a colorless oil; ¹H NMR (C₆D₆) δ 1.37 (ddd, 1H, *J* = 12.0, 9.5, 4.8 Hz), 1.44 (ddd, 1H, *J* = 12.0, 5.7, 3.0 Hz), 1.71 (m, 1H), 1.77 (m, 1H), 1.87 (ddd, 1H, *J* = 12.0, 6.4, 6.4 Hz), 1.94 (ddd, 1H, *J* = 12.0, 12.0, 3.4 Hz), 2.20 (s, 3H), 2.31 (ddd, 1H, *J* = 12.0, 12.0, 5.7 Hz), 2.65 (ddd, 1H, *J* = 12.0, 9.6, 3.5 Hz), 3.00 (dd, 1H, *J* = 6.4, 6.4, 3.0 Hz), 3.40 (dd, 1H, *J* = 9.6, 9.6 Hz), 3.49 (dd, 1H, *J* = 9.6, 3.5 Hz), 3.52 (dd, 1H, *J* = 6.7, 3.0 Hz), 5.33 (s, 2H), 6.12 (dd, 1H, *J* = 8.5, 2.5 Hz), 6.49 (d, 1H, *J* = 2.5 Hz), 6.56 (d, 1H, *J* = 8.5 Hz), 6.79 (dd, 2H, *J* = 8.7, 8.7 Hz), 6.94 (dd, 2H, *J* = 8.7, 5.5 Hz); ¹³C NMR (CDCl₃) δ 154.45, 148.30, 144.66, 139.53, 129.33, 129.20, 115.73, 115.40, 107.98, 105.68,

101.23, 98.14, 70.84, 68.91, 63.28, 62.01, 46.23, 41.55, 41.23, 37.54, 26.10, 22.07. The compound was converted to the *D*-tartrate salt. Recrystallization from EtOH/Et₂O gave a hygroscopic off-white powder: mp 105 °C (fusion); ¹H NMR (CD₃OD) δ 1.95 (m, 1H), 2.13–2.46 (m, 5H), 2.77–3.00 (m, 2H), 2.89 (s, 3H), 3.46–3.70 (m, 2H), 3.99 (m, 1H), 4.14 (m, 1H), 4.43 (s, 2H), 5.84 (s, 2H), 6.15 (dd, 1H), 6.35 (d, 1H), 6.62 (d, 1H), 7.06 (m, 2H), 7.35 (m, 2H); [α]_D²⁰ +32.8° (c 0.29, CH₃OH). Anal. (C₂₆H₃₂FNO₄) C, H, N.

✱ **3a-(4-Fluorophenyl)-2*β*-[[(3,4-methylenedioxy)phenoxy]methyl]tropane [(1*R*)-2*β*-(3a)-7c].** Fractions were pooled to give 0.312 g (42%) of the product as a light yellow oil: ¹H NMR (CD₃OD) δ 1.25 (dd, 1H, *J* = 13.2, 10.8 Hz), 1.50 (ddd, 1H, *J* = 12.5, 9.5, 3.4 Hz), 1.59 (ddd, 1H, *J* = 17.0, 12.1, 4.9 Hz), 1.87 (ddd, 1H, *J* = 10.8, 10.8, 3.5 Hz), 2.13 (ddd, 1H, *J* = 17.0, 12.1, 5.8 Hz), 2.29 (m, 4H), 2.46 (ddd, 1H, *J* = 13.2, 8.6, 8.3 Hz), 2.62 (ddd, 1H, *J* = 10.8, 10.3, 8.3 Hz), 3.29 (m, 2H), 3.59 (dd, 1H, *J* = 10.8, 3.5 Hz), 3.75 (dd, 1H, *J* = 10.8, 10.8 Hz), 5.87 (s, 2H), 6.18 (dd, 1H, *J* = 8.5, 2.5 Hz), 6.38 (d, 1H, *J* = 2.5 Hz), 6.63 (d, 1H, *J* = 8.5 Hz), 6.96 (dd, 1H, *J* = 8.6, 8.6 Hz), 7.16 (dd, 2H, *J* = 8.6, 5.6 Hz); ¹³C NMR (CDCl₃) δ 163.29, 159.39, 154.48, 148.111, 141.39, 140.73, 140.68, 129.47, 129.28, 115.32, 114.99, 107.85, 105.53, 101.05, 97.98, 71.33, 62.73, 59.48, 50.89, 41.45, 41.11, 36.12, 29.43, 28.48. The product was converted to the *D*-tartrate salt. Recrystallization from EtOH/Et₂O gave a hygroscopic off-white solid: mp 84 °C (fusion); ¹H NMR (CD₃OD) δ 1.82 (m, 1H), 2.07–2.19 (m, 2H), 2.30–2.76 (m, 4H), 2.82 (s, 3H), 3.02–3.15 (m, 1H), 3.76 (m, 2H), 3.96 (m, 2H), 5.87 (s, 2H), 6.30 (dd, 1H), 6.51 (d, 1H), 6.65 (d, 1H), 7.07 (m, 2H), 7.35 (m, 2H); [α]_D²⁰ -48.3° (c 0.29, CH₃OH). Anal. (C₂₆H₃₂FNO₄·0.5H₂O) C, H, N.

✱ **(1*S*)-3*β*-(4-Fluorophenyl)-2*β*-[[(3,4-methylenedioxy)phenoxy]methyl]tropane [(1*S*)-2*β*-(3*β*)-7d].** Fractions were pooled to give 1.02 g (69%) of the pure product. ¹H and ¹³C NMR are identical with the (1*R*)-enantiomer. The product was converted to the *D*-tartrate salt. Recrystallization from 2-propanol/ethyl ether yielded a white powder: mp 90 °C (fusion). ¹H and ¹³C NMR are identical with those of the (1*R*)-enantiomer; [α]_D²⁰ -26.8° (c 0.63, CH₃OH). Anal. (C₂₆H₃₂FNO₄) C, H, N.

✱ **(1*S*)-3*β*-(4-Fluorophenyl)-2*α*-[[(3,4-methylenedioxy)phenoxy]methyl]tropane [(1*S*)-2*α*-(3*β*)-7e].** Fractions were pooled to give 0.76 g (64%) of the product as a slightly yellow oil. ¹H and ¹³C NMR are identical with those of the (1*R*)-enantiomer. The compound was converted to the *D*-tartrate salt. Recrystallization from MeOH/Et₂O gave a hygroscopic off-white powder: mp 95 °C (fusion); ¹H and ¹³C NMR are identical with the (1*R*)-enantiomer; [α]_D²⁰ -50.8° (c 0.50, CH₃OH). Anal. (C₂₆H₃₂FNO₄) C, H, N.

✱ **(1*S*)-3*α*-(4-Fluorophenyl)-2*β*-[[(3,4-methylenedioxy)phenoxy]methyl]tropane [(1*S*)-2*β*-(3*α*)-7f].** Fractions were pooled to give 0.24 g (32%) of the product as a light yellow oil. ¹H and ¹³C NMR are identical with those of the (1*R*)-enantiomer. The product was converted to the *D*-tartrate salt. Recrystallization from MeOH/Et₂O gave a hygroscopic white solid: mp 56 °C dec. ¹H and ¹³C NMR are identical with those of the (1*R*)-enantiomer; [α]_D²⁰ +38.2° (c 0.33, CH₃OH). Anal. (C₂₆H₃₂FNO₄·0.25H₂O) C, H, N.

General Procedure for Demethylation of 3-(4-Fluorophenyl)-2-[[(3,4-methylenedioxy)phenoxy]methyl]tropane (7). Method A. The appropriate isomer of 7 (1.0 mmol) was dissolved in 15 mL of dichloroethane under nitrogen gas. Proton Sponge [1.8 bis(dimethylamino)naphthalene, 0.14 mmol; Aldrich] was added, and the solution was stirred for 0.5 h at room temperature. ACE Cl (6.0 mmol) was added, and the reaction mixture was refluxed for 24 h. The reaction mixture was cooled and the solvent removed under reduced pressure. MeOH (10 mL) was added, and the reaction mixture was refluxed for 24 h. The solvent was removed under reduced pressure to afford a dark orange/red oil. Water was added, and the reaction mixture was basified with NH₄OH. The aqueous layer was extracted with CH₂Cl₂. The solvent was removed under reduced pressure, and the product was purified by flash chromatography.

Method B. The appropriate isomer of 7 (1.0 mmol) was dissolved in 10 mL of toluene under nitrogen gas. Potassium carbonate (0.4 mmol) was added, and the solution was refluxed for 0.5 h. Trichloroethyl chloroformate (3.8 mmol) was added, and the reaction was refluxed for 24 h. Additional chloroformate was added, and the reaction was refluxed for 24 h. Water and CHCl₃ were added, and the reaction mixture was basified with NH₄OH. The layers were separated, and the aqueous layer was extracted with CHCl₃. The combined organic layers were dried over Na₂SO₄. The solvent was removed to afford a brown oil. The carboxylate was dissolved in glacial acetic acid (6.0 mL), and Zn dust (1.00 g) was added in small portions. The mixture was stirred for 12 h at room temperature. Water and CHCl₃ were added, and the reaction was filtered through Celite. After basifying with NH₄OH and extracting with CHCl₃, the organic layers were dried over K₂CO₃. The product was purified by flash chromatography on silica gel, first eluting with Et₂O/Et₃N (9:1) followed by CHCl₃/CH₃OH/NH₄OH (90:9:1).

✱ **3*β*-(4-Fluorophenyl)-2*β*-[[(3,4-methylenedioxy)phenoxy]methyl]tropane [(1*R*)-2*β*-(3*β*)-4a]. Method A.** Purification afforded 0.083 g (62%) of the product as a pink oil. ¹H NMR (C₂D₂N₂) δ 1.67 (dd, 1H, *J* = 12.0, 3.5 Hz), 1.91 (m, 2H), 2.05 (ddd, 1H, *J* = 13.9, 10.9, 1.9 Hz), 2.15 (m, 3H), 2.93 (dd, 1H, *J* = 12.3, 1.9 Hz), 3.28 (dd, 1H, *J* = 12.3, 5.5 Hz), 3.32 (m, 2H), 3.60 (dd, 1H, *J* = 10.6, 6.2 Hz), 4.55 (dd, 1H, *J* = 9.5, 5.5, 1.9 Hz), 5.93 (s, 2H), 6.58 (dd, 1H, *J* = 8.4, 2.4 Hz), 6.86 (d, 1H, *J* = 8.4 Hz), 6.87 (d, 1H, *J* = 2.4 Hz), 7.06 (dd, 2H, *J* = 8.7, 8.7 Hz), 7.49 (dd, 2H, *J* = 8.7, 5.4 Hz); ¹³C NMR (CDCl₃) δ 163.18, 159.29, 152.51, 148.34, 142.14, 141.93, 129.11, 128.99, 115.40, 115.06, 108.42, 108.10, 101.18, 99.82, 83.05, 47.72, 46.21, 42.18, 39.84, 33.54, 31.31, 27.02. The product was converted to the *D*-tartrate salt. Recrystallization from EtOH/Et₂O gave a white hygroscopic powder: mp 183–185 °C dec; ¹H NMR (CD₃OD) δ 1.98–2.37 (m, 7H), 3.24–3.42 (m, 2H), 3.72 (m, 1H), 3.87 (br s, 1H), 4.42 (s, 2H), 4.55 (bs, 1H), 5.7 (s, 2H), 6.39 (dd, 1H), 6.58 (d, 1H), 6.68 (d, 1H), 7.05 (m, 2H), 7.33 (m, 2H); [α]_D²⁰ +10.6° (c 0.36, CH₃OH). Anal. (C₂₆H₃₂FNO₄) C, H, N.

✱ **(1*R*)-3*β*-(4-Fluorophenyl)-2*α*-[[(3,4-methylenedioxy)phenoxy]methyl]tropane [(1*R*)-2*α*-(3*β*)-4b]. Method A.** Fractions were pooled to afford 0.19 g (55%) of pink oil. ¹H NMR (C₂D₂N₂) δ 1.68 (m, 3H), 1.78 (m, 1H), 1.87 (dd, 1H, *J* = 12.6, 12.6, 2.2 Hz), 1.97 (m, 1H), 2.58 (m, 1H), 2.73 (dd, 1H, *J* = 11.9, 11.9, 5.5 Hz), 3.58 (ddd, 1H, *J* = 6.6, 3.2, 3.2 Hz), 3.69 (s, 1H), 3.71 (d, 1H, *J* = 1.9 Hz), 3.96 (dd, 1H, *J* = 6.4, 2.2 Hz), 5.90 (s, 2H), 6.32 (dd, 1H, *J* = 8.3, 2.5 Hz), 6.62 (d, 1H, *J* = 2.5 Hz), 6.78 (d, 1H, *J* = 8.3 Hz), 7.11 (dd, 2H, *J* = 8.7, 8.7 Hz), 7.32 (dd, 2H, *J* = 8.7, 5.5 Hz); ¹³C NMR (CDCl₃) δ 163.96, 159.66, 154.13, 148.14, 141.57, 138.91, 129.10, 128.98, 115.66, 115.33, 107.81, 105.44, 101.08, 97.91, 68.57, 56.35, 55.16, 46.48, 46.21, 41.24, 37.89, 28.98, 24.99. The product was converted to the *D*-tartrate salt. Recrystallization from MeOH/Et₂O gave a hygroscopic light yellow powder: mp 140 °C (fusion); ¹H NMR (CD₃OD) δ 1.88–2.45 (m, 6H), 2.66 (m, 1H), 3.00 (1H), 3.53–3.70 (m, 2H), 4.13 (m, 1H), 4.28 (m, 1H), 4.42 (s, 2H), 5.84 (s, 2H), 6.14 (dd, 1H), 6.34 (d, 1H), 6.60 (d, 1H), 7.06 (m, 2H), 7.33 (m, 2H); [α]_D²⁰ +36.4° (c 0.30, CH₃OH). Anal. (C₂₆H₃₂FNO₄·0.5H₂O) C, H, N.

✱ **(1*R*)-3*α*-(4-Fluorophenyl)-2*β*-[[(3,4-methylenedioxy)phenoxy]methyl]tropane [(1*R*)-2*β*-(3*α*)-4c]. Method A.** Fractions were pooled to afford 0.069 g (55%) of yellow oil. ¹H NMR (C₂D₂N₂) δ 1.51 (m, 1H), 1.65 (m, 2H), 1.92 (m, 2H), 2.23 (ddd, 1H, *J* = 13.8, 9.1, 7.4 Hz), 2.80 (ddd, 1H, *J* = 11.1, 11.1, 7.4 Hz), 3.52 (m, 2H), 3.71 (d, 1H, *J* = 3.3 Hz), 3.75 (dd, 1H, *J* = 9.1, 3.7 Hz), 3.91 (dd, 1H, *J* = 9.1, 9.1 Hz), 5.85 (s, 2H), 6.35 (dd, 1H, *J* = 8.4, 2.3 Hz), 6.65 (d, 1H, *J* = 2.4 Hz), 6.77 (d, 1H, *J* = 8.5 Hz), 7.09 (dd, 1H, *J* = 8.6 Hz), 7.25 (dd, 1H, *J* = 8.4, 5.6 Hz); ¹³C NMR (CDCl₃) δ 163.61, 154.52, 148.07, 141.62, 140.39, 129.47, 115.37, 115.03, 107.87, 105.60, 101.38, 98.03, 71.11, 55.25, 51.96, 49.84, 39.12, 35.92, 34.33, 32.30. The product was converted to the *D*-tartrate salt. Recrystallization from 2-propanol/Et₂O gave a hygroscopic white crystalline solid, mp 174 °C dec; ¹H NMR (CD₃OD) δ 1.72 (m, 1H),

2.01–2.24 (m, 5H), 2.58 (m, 1H), 2.94 (m, 1H), 3.69 (m, 2H), 4.11 (m, 2H), 5.86 (s, 1H), 62.8 (dd, 1H), 6.50 (d, 1H), 6.65 (d, 1H), 7.06 (m, 2H), 7.33 (m, 2H); $[\alpha]_D^{20}$ –79.7° (c 0.32, CH₂OH). Anal. (C₂₅H₂₈FNO₄) C, H, N.

✱ **(1*S*)-3-(4-Fluorophenyl)-2*β*-(13,4-(methylenedioxy)-phenoxy)methyl nor tropane (1*S*)-2*β*,3*β*-4*d*). Method B. Flash chromatography gave 0.098 g (26%) of the product. Another fraction contained 0.118 g of the *N*-methyl starting material. ¹H and ¹³C NMR are identical with the (1*R*)-enantiomer. The product was converted to the *L*-tartrate salt. Recrystallization from EtOH/Et₂O gave a light tan hygroscopic powder: mp 180–184 °C dec; ¹H and ¹³C NMR are identical with those of the (1*R*)-enantiomer; $[\alpha]_D^{20}$ –10.3° (c 0.30, CH₂OH). Anal. (C₂₅H₂₈FNO₄) C, H, N.**

✱ **(1*S*)-3-(4-Fluorophenyl)-2*α*-(13,4-(methylenedioxy)-phenoxy)methyl nor tropane (1*S*)-2*α*,3*β*-4*e*). Method A. Fractions were pooled to afford 0.135 g (40%) of pink oil. ¹H and ¹³C NMR are identical with those of the (1*R*)-enantiomer. The product was converted to the *D*-tartrate salt. Recrystallization from MeOH/Et₂O gave a hygroscopic tan powder: mp 170 °C (fusion); ¹H and ¹³C NMR are identical with those of the (1*R*)-enantiomer; $[\alpha]_D^{20}$ –52.4° (c 0.50, CH₂OH). Anal. (C₂₅H₂₈FNO₄·0.25H₂O) C, H, N.**

✱ **(1*S*)-3-(4-Fluorophenyl)-2*β*-(13,4-(methylenedioxy)-phenoxy)methyl nor tropane (1*S*)-2*β*,3*β*-4*d*). Method B. Flash chromatography afforded 0.095 g (55%) of the product as a brown oil. ¹H and ¹³C NMR are identical with those of the (1*R*)-enantiomer. The product was converted to the *L*-tartrate salt. Recrystallization from EtOH/Et₂O gave a light tan hygroscopic powder: mp 163–166 °C dec; ¹H and ¹³C NMR are identical with those of the (1*R*)-enantiomer; $[\alpha]_D^{20}$ +76.3° (c 0.27, CH₂OH). Anal. (C₂₅H₂₈FNO₄·0.5H₂O) C, H, N.**

(1*R*)-3-(4-Fluorophenyl)-2*α*-(3-methyl-1,2,4-oxadiazol-5-yl)tropane (10). To a cooled solution (–78 °C) of bromofluorobenzene (0.64 g, 3.66 mmol) in 10 mL of anhydrous Et₂O was added *n*-BuLi (1.0 M in pentane, 6.0 mL, 6.00 mmol) dropwise. After the mixture was stirred for 20 min at –78 °C, a solution of **9** (0.31 g, 1.51 mmol) in 20 mL of Et₂O was added slowly. The reaction was stirred at –78 °C for 2 h and then at –40 °C for 1 h. The reaction was treated with ethereal THF over 5 min, allowed to warm to 0 °C, and diluted with ether. The mixture was basified with dilute NH₄OH and the layers were separated. After the organic layer was dried over Na₂SO₄, the solvent was removed to give 0.44 g of oil. Flash chromatography [EtOAc/Et₂N/hexanes (2.7:3:70)] gave 0.28 g of product as a white solid. Recrystallization from hexanes afforded 0.158 g (35%) of white crystals: mp 101–103 °C; ¹H NMR (CDCl₃) δ 1.52–1.67 (m, 2H), 1.83–2.15 (m, 3H), 2.25 (s, 3H), 2.32 (s, 1H), 2.47 (m, 1H), 3.35 (m, 1H), 3.56 (m, 1H), 3.65 (m, 1H), 4.18 (m, 1H), 6.84 (m, 2H), 7.06 (m, 2H); ¹³C NMR (CDCl₃) δ 179.41, 166.49, 137.41, 129.28, 129.16, 114.89, 114.59, 62.24, 59.63, 44.31, 40.48, 35.33, 34.69, 28.39, 23.10, 11.49; $[\alpha]_D^{20}$ +52.0° (c 0.60, CHCl₃). Anal. (C₁₇H₂₀FNO₃) C, H, N.

✱ **(1*R*)-3-(4-Fluorophenyl)-2*β*-carbomethoxytropane (1*R*)-2*β*,3*α*-5*i*). To a solution of nickel acetate (5.33 g, 21.43 mmol) in 50 mL of MeOH was added slowly a slurry of NaBH₄ (0.801 g, 21.43 mmol) in 25 mL of MeOH. A solution of the oxadiazolyltropane **10** (1.29 g, 4.28 mmol) and HCl (12 N, 1.78 mL, 21.43 mmol) in 50 mL of MeOH was added slowly to the black slurry. The reaction mixture was stirred at room temperature for 2 h and then refluxed for 3 h. The reaction mixture was cooled and then Et₂O and saturated NaHCO₃ were added. The reaction was basified with NH₄OH to pH 10. The layers were separated, and the blue aqueous layer was extracted with Et₂O several times. The solvent was removed to afford 1.03 g of clear oil. ¹H NMR (C₆D₆) δ 1.03–1.18 (m, 2H), 1.27–1.33 (m, 1H), 1.70–1.92 (m, 2H), 2.02 (s, 3H), 2.25 (m, 1H), 2.38 (m, 1H), 2.88 (m, 1H), 3.25 (s, 3H), 3.31 (m, 1H), 3.55–3.66 (m, 1H), 6.77 (m, 2H), 6.91 (m, 2H). The ester was characterized as the *p*-tartrate salt:¹⁷ $[\alpha]_D^{20}$ –34.4° (c 0.54, CH₂OH); mp 65 °C. Anal. (C₂₀H₂₆FNO₄·0.5H₂O) C, H, N.**

(1*S*)-2-Carbomethoxy-3-[(trifluoromethyl)sulfonyl]-oxytropane (12). Carbomethoxytropane^{19,45,43} (6.01 g, 30.5 mmol) was dissolved in 150 mL of anhydrous THF under N₂. After the mixture was cooled to –78 °C, bis(trimethylsilyl)-amide (1.0 M solution in THF, 40.0 mL, 40.0 mmol) was added dropwise by an addition funnel. The mixture was stirred at –78 °C for 0.5 h. The triflimide (13.03 g, 36.5 mmol) was dissolved in 100 mL of anhydrous THF and added dropwise. The reaction was stirred for 10 min at –78 °C, then warmed to 0 °C, and stirred for 2 h. The reaction vessel was fitted with a drying tube and allowed to remain at 5 °C for 36 h. The reaction was quenched with H₂O and extracted with CH₂Cl₂. After the mixture was dried over Na₂SO₄, solvent was removed from the solution to afford 11.77 g of brown oil. Purification by flash chromatography (hexane/EtOAc, 3:2) gave 8.07 g (80%) of triflate **12** as a golden oil: ¹H NMR (CDCl₃) δ 1.60 (m, 1H), 2.00 (m, 2H), 2.40 (s, 3H), 2.40 (s, 3H), 2.85 (m, 1H), 3.43 (m, 1H), 3.82 (s, 3H), 3.93 (d, 1H), ¹³C NMR (CDCl₃) δ 163.79, 149.10, 125.19, 118.21 (q), 60.08, 57.40, 52.05, 34.86, 34.66, 33.03, 29.96; $[\alpha]_D^{20}$ –7.8° (c 1.0, CHCl₃). Anal. (C₁₆H₁₈F₃O₅S) C, H, N.

(1*S*)-Anhydrocogaine Methyl Ester (13). The triflate **12** (11.36 g, 34.5 mmol) was dissolved in 250 mL of anhydrous THF under N₂. Next, Pd(OAc)₂ (0.177 g, 0.788 mmol), PPh₃ (0.461 g, 1.76 mmol), and Et₃N (14.4 mL, 10.45 g, 103.3 mmol) were added. The reaction was stirred for 5 min, HCO₂H (2.60 mL, 3.17 g, 68.9 mmol) was added dropwise, and the mixture was refluxed for 1 h. After to room temperature, water was added. The reaction was extracted with CHCl₃ and dried over Na₂SO₄. Purification by flash chromatography (Et₂O/Et₃N/hexane, 9:1:10) gave 5.43 g (87%; 75%, 2 steps from **11**) of **13**: ¹H NMR (CDCl₃) δ 1.49 (m, 1H), 1.86 (m, 2H), 2.14 (m, 2H), 2.34 (s, 3H), 2.62 (m, 1H), 3.24 (m, 1H), 3.74 (s, 3H), 3.79 (m, 1H), 6.82 (m, 2H); $[\alpha]_D^{20}$ +35.5° (c 1.0, CHCl₃) [lit.⁴³ $[\alpha]_D^{20}$ +38.3° (c 1.0, CH₂OH)].

(1*S*)-3-(4-Fluorophenyl)tropane-2*β*-carboxylic Acid Methyl Ester (1*S*)-2*β*,3*β*-5*i*. The synthesis of this compound has been described previously.⁴³ The fractions were pooled to give 4.22 g (51%) of product as a white solid: mp 92–93 °C [lit.⁴³ mp 94–96 °C]. A second fraction (1.48 g) contained the *l*-isomer: ¹H NMR (CDCl₃) δ 7.22 (m, 2H), 6.95 (m, 2H), 3.57 (m, 1H), 3.50 (s, 3H), 3.36 (m, 1H), 2.95 (m, 1H), 2.86 (m, 1H), 2.57 (m, 1H), 2.22 (s, 3H), 2.15 (m, 2H), 1.57–1.75 (m, 3H); $[\alpha]_D^{20}$ +49.2° (c 0.52, CH₂OH) [lit.⁴³ for the naphthalene-1,5-disulfonate $[\alpha]_D^{20}$ +84.5° (c 1.0, H₂O)].

(1*S*)-3-(4-Fluorophenyl)tropane-2*α*-carboxylic Acid Methyl Ester (1*S*)-2*α*,3*β*-5*i*. A white solid was obtained which was recrystallized to give white crystals: mp 68–70 °C [lit.⁴³ mp 71.5–73.5 °C]; ¹H NMR (CDCl₃) δ 1.56–1.25 (m, 6H), 2.40 (s, 3H), 3.00–3.14 (m, 2H), 3.23 (m, 1H), 3.41 (m, 1H), 3.50 (s, 3H), 6.97 (m, 2H), 7.21 (m, 2H); ¹³C NMR (CDCl₃) δ 173.30, 161.40 (d), 139.38, 129.19, 129.07, 115.30, 114.97, 63.62, 61.12, 51.49, 51.42, 39.65, 38.76, 36.14, 26.40, 23.20; $[\alpha]_D^{20}$ –14.5° (c 0.55, CH₂OH) [lit.⁴³ $[\alpha]_D^{20}$ –1.2° (c 5.0, CH₂OH)].

(1*S*)-2-Carbomethoxy-3-(4-fluorophenyl)tropane (14). To a round-bottom flask was added the triflate **12** (1.51 g, 4.59 mmol), LiCl (0.402 g, 9.57 mmol), tris(dibenzylacetone)-dipalladium(0) (0.170 g), Na₂CO₃ (2.0 M soln in H₂O, 4.5 mL, 9.0 mmol), and diethoxymethane (10 mL). The mixture was stirred vigorously, and (*p*-fluorophenyl)boronic acid (0.852 g, 6.08 mmol) was added. The reaction was refluxed and monitored by TLC (Et₂O/Et₃N, 9:1). After 1 h, the reaction was filtered through Celite. Et₂O and H₂O were added, and the mixture was basified to pH 10 with NH₄OH. The layers were separated, and the aqueous layer was extracted with CHCl₃. The organic layers were combined and dried over Na₂SO₄. The solvent was removed from the dried solution to afford a dark yellow oil. Purification of the residue by flash chromatography (silica gel, Et₂O/Et₃N/hexane, 9:1:10) afforded 1.09 g (86%) of the tropane as a yellow oil which solidified upon standing: mp 56–58 °C; ¹H NMR (CDCl₃) δ 7.13–6.97 (m, 4H), 3.85 (d, 1H), 3.50 (s, 3H), 3.35 (m, 1H), 2.74 (m, 1H), 2.44 (s, 3H), 1.94–2.24 (m, 4H), 1.64 (m, 1H); ¹³C NMR (CDCl₃) δ 168.21, 162.12 (d), 142.77, 137.15, 131.02, 128.52, 128.40,

115.15, 114.81, 60.35, 57.45, 51.36, 37.82, 36.14, 34.21, 30.13; $[\alpha]_D^{20} +61.7^\circ$ (c 0.86, CHCl_3). Anal. ($\text{C}_{16}\text{H}_{19}\text{FNO}_3$) C, H, N. (1*S*)-3-(4-Fluorophenyl)tropane-2*-carboxylic Acid Methyl Ester* [(1*S*)-2*b*, 3*a*]. Tropene 14 (0.93 g, 3.38 mmol) was dissolved in 5 mL of anhydrous MeOH under argon. After the solution was heated to 40 °C, the SnCl_4 solution (0.1 M in THF, 140 mL, 14.0 mmol) was added dropwise via syringe. The mixture was stirred at 40 °C and monitored by TLC [$\text{Et}_2\text{O}/\text{Et}_3\text{N}$ (9:1)]. After 1.0 h, the reaction was quenched by the dropwise addition of a 10% HCl solution. Water and Et_2O were added, and the mixture was basified to pH 11 with NH_4OH and filtered through Celite. Et_2O and saturated $\text{Na}_2\text{S}_2\text{O}_5$ were added, and the layers were separated. The aqueous layer was extracted with CHCl_3 . The organic layers were combined and dried over Na_2SO_4 . Solvent was removed from the dried solution to afford a yellow oil. Purification of the residue by flash chromatography (2.5% $\text{EtOH}/\text{CHCl}_3$) and $\text{Et}_2\text{O}/\text{Et}_3\text{N}/\text{hexane}$, 9:1:10 gave the desired 2*b*, 3*a* isomer (45%) along with 14% of the 2*b*, 3*b* isomer: ^1H NMR (CDCl_3) δ 7.16 (m, 2H), 6.93 (m, 2H), 3.58 (s, 3H), 3.28 (m, 3H), 2.42 (m, 2H), 2.38 (s, 3H), 2.19 (m, 2H), 1.47–1.64 (m, 2H), 1.31 (m, 1H); ^{13}C NMR (CDCl_3) δ 6.91 (m, 2H), 6.77 (m, 2H), 3.59 (m, 1H), 3.31 (m, 1H), 3.25 (s, 3H), 2.88 (m, 1H), 2.38 (m, 1H), 2.28 (m, 1H), 2.01 (s, 3H), 1.73–1.92 (m, 2H), 1.28 (m, 1H), 1.03–1.17 (m, 2H); ^{13}C NMR (CDCl_3) δ 175.34, 161.62 (d), 139.91, 129.43, 129.31, 115.49, 115.16, 63.38, 59.66, 57.03, 52.01, 41.29, 39.72, 35.99, 29.38, 29.26.

The compound was characterized as the L-tartaric acid salt: mp 90–95 °C (fusion); ^1H NMR (CD_3OD) δ 1.81 (m, 1H), 2.11 (m, 2H), 2.51 (m, 1H), 2.63 (m, 1H), 2.70 (m, 1H), 2.81 (s, 3H), 3.45 (m, 2H), 3.95 (m, 2H), 4.47 (s, 3H), 7.05 (m, 2H), 7.48 (m, 2H); $[\alpha]_D^{20} +47.8^\circ$ (c 0.27, CH_3OH). Anal. ($\text{C}_{20}\text{H}_{25}\text{FNO}_6$) C, H, N.

Acknowledgment. This work was supported in part by the National Institute on Drug Abuse, Grant Number DA05477.

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JM970669P



Source: USPQ, 2d Series (1986 - Present) > U.S. Court of Appeals, Federal Circuit > Sanofi-Synthelabo v. Apotex Inc., 89 USPQ2d 1370 (Fed. Cir. 2008)

89 USPQ2d 1370
Sanofi-Synthelabo v. Apotex Inc.
U.S. Court of Appeals
Federal Circuit

No. 2007-1438

Decided December 12, 2008

550 F3d 1075

Headnotes

PATENTS

[1] Patentability/Validity — Anticipation — Identity of elements (► 115.0704)

Patentability/Validity — Specification — Enablement (► 115.1105)

Federal district court did not clearly err in finding that two prior art patents disclosing "racemate PCR 4099," which is combination of dextrorotatory and levorotatory enantiomers of specific compound, do not anticipate invention of claim in patent for clopidogrel compositions used in blood platelet aggregation inhibiting agent, which recites bisulfate salt of dextrorotatory enantiomer of same compound substantially separated from its levorotatory enantiomer, since disclosure of genus in prior art is not necessarily disclosure of every species within its scope, since references state generally that racemate compounds consist of enantiomers, but nothing in reference disclosure would have led person of ordinary skill in art to recognize either explicit or inherent disclosure of racemate's dextrorotatory enantiomer and its bisulfate salt, and since knowledge that enantiomers exist, and that they may be separated, is not "anticipation" of specific enantiomer that has not been separated, identified, and characterized; district court did not clearly err in finding that asserted patents are not enabling, since references contain no guidance on how to separate enantiomers of PCR 4099, and undue experimentation thus would have been required to obtain claimed invention.

[2] Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (► 115.0903.03)

Patentability/Validity — Obviousness — Combining references (► 115.0905)

Federal district court did not clearly err in finding that claim of patent for clopidogrel compositions used in blood platelet aggregation inhibiting agent, which recites bisulfate salt of dextrorotatory enantiomer of specific compound substantially separated from its levorotatory enantiomer, is not invalid for obviousness over prior art references that disclose "racemate PCR 4099," from which dextrorotatory enantiomer may be separated, since record supports court's findings that person of ordinary skill in art would not reasonably have predicted from reference disclosure that dextrorotatory enantiomer would provide desired antiplatelet activity without adverse neurotoxicity, that separation of enantiomers was not simple or routine procedure, and that success in separation, as well as allocation of properties, was unpredictable, and since patent in suit claims bisulfate salt, whereas PCR 4099 racemate is hydrochloride, and both parties' experts agreed that whether pharmaceutically suitable crystalline salt will form from particular acid-base combination is unpredictable; present case does not involve "combination of familiar elements according to known methods" that "does no more than yield predictable results."

Particular Patents

Particular patents — Chemical — Clopidogrel compositions

4,847,265, Badore and Frehel, dextro-rotatory enantiomer of methyl alpha-5 (4,5,6,7-tetrahydro (3,2-c) thienopyridyl) (2-chlorophenyl)-acetate and the pharmaceutical compositions containing it, judgment that patent is enforceable and not invalid affirmed.

Case History and Disposition

Appeal from the U.S. District Court for the Southern District of New York, Stein, J.

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Action by Sanofi-Synthelabo, Sanofi-Synthelabo Inc., and Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership against Apotex Inc. and Apotex Corp. for patent infringement under 35 U.S.C. §271(e)(2), in which defendants counterclaimed for declaratory judgment of invalidity, unenforceability, and noninfringement. District court granted plaintiffs' motion for preliminary injunction, which was affirmed on appeal (81 USPQ2d 1097). Following bench trial, district court found patent valid and enforceable, and defendants appealed. Affirmed.

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Judge

Before Newman, Lourie, and Bryson, circuit judges.

Opinion Text

Opinion By:

Newman, J.

This suit arose in accordance with the provisions of the Hatch-Waxman Act, codified at 35 U.S.C. §271 (e) and 21 U.S.C. §355(j). The patent at issue is United States Patent No. 4,847,265 (the '265 patent), owned by Sanofi-Synthelabo and related companies (collectively "Sanofi"), and covers the pharmaceutical product having the common name clopidogrel bisulfate and the brand name Plavix®. The product has the property of inhibiting the aggregation of blood platelets, and is used to treat or prevent blood-thrombotic events such as heart attacks and strokes. We affirm the district court's ruling sustaining patent validity.

BACKGROUND

Clopidogrel is the common name of the dextrorotatory isomer of the chemical compound named methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate. Claim 3 of the patent is in suit:

3. Hydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5 (4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

The '265 patent was issued on July 11, 1989, with priority from an application first filed in France in 1987. Approval of the product by the United States Food and Drug Administration (FDA) was received in 1998.

Apotex, Inc. filed an Abbreviated New Drug Application (ANDA) ¹ in November 2001 for FDA approval to sell clopidogrel bisulfate, stating, pursuant to 21 U.S.C. §355(j)(2)(A)(vii)(IV), that it believed the '265 patent to be invalid. Such "paragraph IV certification" is defined as an act of infringement for litigation purposes, 35 U.S.C. §271(e), in order to facilitate pre-marketing legal challenge by the producer of a generic form of a patented pharmaceutical product. In accordance with the statutory procedures Sanofi duly filed suit for infringement, and Apotex counterclaimed that the '265 patent is invalid on several grounds and unenforceable. The suit initiated a thirty-month stay of FDA approval of Apotex's ANDA, as provided by 21 U.S.C. §355(j)(5)(B)(iii). A proposed settlement was not achieved, the statutory stay expired, the FDA approved the Apotex ANDA, and Apotex commenced sale of its

generic clopidogrel bisulfate product on August 8, 2006. Sanofi then moved in the district court for a preliminary injunction, asking that Apotex be enjoined from marketing its infringing product while the litigation was pending, noting that infringement was conceded by Apotex.

¹ Federal approval of a generic counterpart of a previously approved drug pursuant to an ANDA requires showing that the generic product is the same as the approved product; evidence of safety and efficacy of the generic product is not required. See 21 U.S.C. §§355(j)(2)(A) and 355(b)(1).

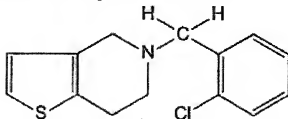
The district court found that Sanofi was likely to succeed on the merits of the validity and enforceability of the '265 patent, and that the equitable factors of the balance of harms, the probability of irreparable harm, and the various public interests, favored granting the injunction. *Sanofi-Synthelabo v. Apotex Inc.*, 488 F.Supp.2d 317, 350 (S.D.N.Y. 2006) ("*Sanofi I*"). This court affirmed the district court's rulings, while explaining that the record on the substantive issues was necessarily incomplete and that the district court could review all aspects at trial. See *Sanofi-Synthelabo v. Apotex Inc.*, 470 F.3d 1368, 1374-84 [81 USPQ2d 1097] (Fed. Cir. 2006) ("*Sanofi II*") (holding that the patentee was likely to succeed on the merits, and that the balance of hardships and public interest supported

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the injunction). A bench trial was held from January 22 to February 15, 2007, following which the district court ruled that the '265 patent is valid and enforceable. *Sanofi-Synthelabo v. Apotex Inc.*, 492 F.Supp.2d 353, 397 (S.D.N.Y. 2007) ("*Sanofi III*").

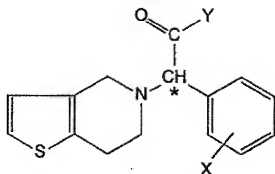
This appeal is focused on the question of patentability of this dextrorotatory isomer in view of its known racemate described in earlier Sanofi patents, specifically, Sanofi's United States Patent No. 4,529,596 (the '596 patent) and Canadian Patent No. 1,194,875 (the '875 patent). Both reference patents are derived from the same French priority filing and are prior art against the '265 patent.

The activities that led to the product in suit are discussed in the earlier opinions, and are summarized as relevant herein: In 1972 Sanofi scientists were seeking products that might have improved anti-inflammatory properties, and in the course of this work discovered that certain compounds of the class known as thienopyridines (compounds having a thiene ring fused to a pyridine ring) have the property of inhibiting blood platelet aggregation. Sanofi scientists, led by Dr. Jean-Pierre Maffrand, pursued this direction of research. The record states that they initially synthesized and evaluated several hundred chemical modifications and derivatives of thienopyridines, seeking optimum anti-platelet aggregation properties with minimal undesirable effects. They eventually selected for development the compound having the following structural formula:

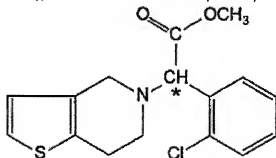


Sanofi gave this compound the common name "ticlopidine." After lengthy development, including animal and human trials, in 1991 ticlopidine was approved in the United States for use as an anti-thrombotic agent. This approval, however, was accompanied by required warnings concerning possible adverse effects, for reports had been received of rarely occurring but serious blood disorders, neutropenia and thrombotic thrombocytopenic purpura, associated with prolonged usage of ticlopidine. Thus Sanofi continued its search for a product that would have the therapeutic benefits of ticlopidine but without the adverse properties.

Sanofi synthesized and evaluated several hundred additional thienopyridine derivatives, including a class of compounds having the following general structure, wherein one of the hydrogen atoms on the bridge carbon atom (marked with an asterisk), is replaced with an ester, carboxylic acid, or amide group. This class is the subject of the '596 patent (and the counterpart Canadian '875 patent), and is shown as follows:



X and Y can be any of a number of substituents, as identified in the patents; the district court found that there are thirty-seven possibilities for X and 1710 choices for Y. The patents state that compounds of this class exhibit good anti-platelet aggregation properties and are well tolerated. Focusing on the '596 patent, the specification includes twenty-one examples of specific compounds, including a compound designated as PCR 4099, which Sanofi synthesized in July 1980. In PCR 4099 the substituent attached to the bridge carbon is the methyl ester group (-COOCH₃), and X is chlorine in the 2-position, as follows:



This compound has the chemical name methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl)(2-chlorophenyl)-acetate, with the acronym MATTPCA. PCR 4099 as the hydrochloride salt was selected for commercial development as a potential replacement for ticlopidine in light of its improved platelet inhibition and toxicity profile.

However, PCR 4099 still raised toxicity concerns, for at very high doses it caused convulsions in laboratory animals. Thus the research efforts continued, concurrently with the clinical and commercial development of PCR 4099. Sanofi states that about 1500 compounds

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in this general class were synthesized, of which about 600, including PCR 4099, were chiral thienopyridines. "Chiral" is defined as "describ[ing] asymmetric molecules that are mirror images of each other, i.e., they are related like right and left hands. Such molecules are also called enantiomers and are characterized by optical activity." Richard J. Lewis, Sr., *Hawley's Condensed Chemical Dictionary* 270 (15th ed. 2007).

Enantiomers are spatial isomers, also called stereoisomers, wherein the isomeric compounds have the same chemical formula and the same chemical structure, but differ in their orientation in three-dimensional space. Such stereoisomers can exist for all molecules that contain an asymmetric carbon atom. An "asymmetric carbon" is a carbon atom to which four different substituents are attached, whereby, due to the tetrahedral structure of carbon bonds in three dimensions, the spatial orientation of substituents attached to a carbon atom varies. When there is only one asymmetric carbon atom in the molecule and thus only two stereoisomers, these isomers are called enantiomers.

Enantiomers are identified and distinguished by their optical characteristics when a purified solution of the separated isomers is exposed to plane-polarized light. One enantiomer will rotate plane-polarized light to the right (and thus is called the dextrorotatory or *d*- or (+) isomer), and the other rotates plane-polarized light to the left (called the levorotatory or *l*- or (-) isomer). For the compounds here at issue, the asymmetric carbon is at the bridge between the thienopyridine and the benzene components of the molecule, as marked with an asterisk in the drawings shown *ante*. Enantiomers generally are formed in equal amounts, to produce what is called a racemate; the racemate is

optically neutral.

In the district court, experts for both sides explained the difficulty of separating enantiomers, for they are identical except for the spatial arrangement at one of the carbon atoms. Sanofi scientists had previously separated the enantiomers of two thienopyridines, and had found that the separated enantiomers showed no advantage over the racemates. The first such separation was conducted in 1978 for a compound designated PCR 1033, which had a methyl group in place of one of the hydrogen atoms on the bridge carbon of ticlopidine, and whose maleate salt was found to be more potent than ticlopidine in antiplatelet activity but had undesirable side effects. On separation, it was found that one of the enantiomers of PCR 1033 was more biologically active but also more neurotoxic than the racemate. Thus, separation offered no benefit for PCR 1033.

About three years later, Sanofi separated the enantiomers of a compound designated PCR 3233, which had an ethyl group on the bridge carbon, and was more effective in antiplatelet activity than ticlopidine. However, neither of the separated enantiomers differed in activity from the racemate, and thus separation offered no benefit for PCR 3233. Sanofi witnesses testified to their belief that there was no advantage to separation of the enantiomers of thienopyridines, and no other racemates were separated until, in November 1985, Dr. Maffrand decided to study the enantiomers of PCR 4099.

The separation for PCR 4099 was assigned to Mr. Alain Badorc, the chemist who had separated the enantiomers of PCR 1033 and 3233. It was explained in the district court that such separations are complex and time-consuming, for enantiomers are identical except for the spatial orientation about one carbon atom, and tend to have identical or almost identical chemical and physical properties. The district court received testimony that although the chemical literature shows at least ten separation techniques that might be tried, it cannot be known in advance which, if any, technique might work.

The record shows five months of experimentation by Mr. Badorc, and eventually the successful separation using a technique called diastereomeric salt formation. This procedure, which originated with Louis Pasteur, is based on the trial of diverse salt-forming compositions and conditions, in the hope of coming upon a lucky combination of reagents that will preferentially select one of the enantiomers and crystallize from the solution in optically pure form. In Mr. Badorc's successful experiment, he prepared thirty compositions of PCR 4099 and various resolving acids at various concentrations and in various solvents, and after about one month crystals formed in the composition containing (+)camphorsulfonic acid and PCR 4099 in a 4:10 ratio, dissolved in acetone. This combination eventually yielded the pure levorotatory enantiomer, and isolation of the pure dextrorotatory enantiomer followed, as discussed by the district court in *Sanofi III*, 492 F.Supp.2d at 372-73.

Sanofi then determined the biological properties of the enantiomers of PCR 4099, and found that they had the rare characteristic of

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"absolute stereoselectivity": the dextrorotatory enantiomer provided all of the favorable antiplatelet activity but with no significant neurotoxicity, while the levorotatory enantiomer produced no antiplatelet activity but virtually all of the neurotoxicity. The experts for both sides agreed that while it was generally known that enantiomers can exhibit different biological activity, this degree and kind of stereoselectivity is rare, and could not have been predicted. The experts explained that in the usual case, if one enantiomer is more biologically active than the other, that activity includes the adverse as well as the beneficial properties.

In view of these results, in April 1987 Sanofi terminated commercial development of the racemate PCR 4099, which had been proceeding since 1980 and had reached Phase I human trials at a cost stated to be tens of millions of dollars. More years of development ensued for the dextrorotatory enantiomer, to which Sanofi gave the common name "clopidogrel." Sanofi also found that the hydrochloride salt, which had been suitable for processing and tableting the racemate PCR 4099, was not suitable for clopidogrel. After further research, Sanofi found that the hydrogen sulfate salt (also called the bisulfate) was suitable for tableting. FDA approval of clopidogrel bisulfate was achieved in the United States in 1998, allowing introduction of the product Plavix®.

Sanofi filed a patent application directed to clopidogrel and certain salts and pharmaceutical compositions, in France on February 17, 1987 and then in the United States and other countries. The United States patent is the '265 patent in suit. The '265 specification explains that the racemate of the same chemical formula was described in the earlier French '247 patent, which corresponds to the earlier U.S. '596 patent. The '265 patent discusses the unusual stereoselectivity of the biological

properties as between the dextrorotatory and the levorotatory enantiomers. The United States patent examiner, who had also examined the '596 patent, allowed the claims after requiring that the '265 claims make clear that the dextro- and levo- enantiomers are "substantially separated."

Apotex stipulated that claim 3 of the '265 patent is literally infringed by its product. The district court, after full trial including extensive expert testimony provided by both sides, ruled that claim 3 is valid and enforceable. Apotex appeals the court's rulings on the issues of anticipation and obviousness; the rulings in Sanofi's favor on the issues of unenforceability and double patenting are not appealed.

ANTICIPATION

Claimed subject matter is "anticipated" when it is not new; that is, when it was previously known. Invalidation on this ground requires that every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention. See *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1379 [67 USPQ2d 1664] (Fed. Cir. 2003); *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1267-69 [20 USPQ2d 1746] (Fed. Cir. 1991). An anticipating reference must be enabling; that is, the description must be such that a person of ordinary skill in the field of the invention can practice the subject matter based on the reference, without undue experimentation. See *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1306-07 [79 USPQ2d 1705] (Fed. Cir. 2006); *Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1054 [68 USPQ2d 1373] (Fed. Cir. 2003). Anticipation is a question of fact, and the district court's finding of this issue is reviewed for clear error. See *Merck & Co. v. Teva Pharms. USA, Inc.*, 347 F.3d 1367, 1369 [68 USPQ2d 1857] (Fed. Cir. 2003).

A

The district court identified the limitations stated in claim 3 of the '265 patent as (1) the bisulfate salt of (2) the dextrorotatory enantiomer of (3) the compound MATTPCA (4) substantially separated from the levorotatory enantiomer. The references on which Apotex relied were the '596 patent or its Canadian '875 counterpart. Apotex argued that either reference not only shows the racemate PCR 4099, but also its addition salts and enantiomeric forms. The district court discussed that these references show PCR 4099 only as the racemate, and do not show the separated enantiomer or the bisulfate salt thereof. The district court found that although the racemate is in the prior art, the dextrorotatory enantiomer and salt in claim 3 of the '265 patent are not described, either explicitly or inherently, in any reference.

The court heard expert witnesses for both sides, who agreed that persons of ordinary skill in this field would have known that compounds that contain an asymmetric carbon

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atom have enantiomers. The '596 specification states: "These compounds having an asymmetrical carbon may exist in the form of two enantiomers. The invention relates both to each enantiomer and their mixture." '596 patent, col. 1, lines 39-41. However, as the witnesses agreed, all of the compounds in the '596 patent are racemates, and neither the twenty-one specific examples nor any other part of the specification shows their separation into enantiomers. The district court reasoned that a person of ordinary skill in the field of the invention would not have been guided to either the dextrorotatory enantiomer of PCR 4099 or its bisulfate salt.

Apotex argues that the district court erred in law, and that it suffices that the reference shows the specific racemate PCR 4099 and states that the compounds in the reference have enantiomers and that the enantiomers are included in the invention. Apotex states that the separation of enantiomers is routine, even if time-consuming or requiring some experimentation, and thus that the separation need not have been performed or described in the reference. Apotex states that the properties of the enantiomers of PCR 4099 are inherently and necessarily present in its known racemate, such that when the enantiomers are separated the previously observed properties are "immediately recognized" in one or the other enantiomer.

Apotex stresses that the '596 patent's Example 1 is specific to PCR 4099, and the '596 claims refer to "addition salts with pharmaceutically acceptable mineral or organic acids" and "both enantiomeric forms or their mixture." The counterpart Canadian '875 patent states that when the desired structure is obtained it "is isolated and, if desired, its enantiomers are separated and/or it is saltified by mineral or organic acid action." Apotex concedes that the references do not show any separated enantiomers or describe how to separate them, but argues that such detail is not required because persons of ordinary skill would know the existing techniques for separating enantiomers. Apotex thus argues that

the dextrorotatory enantiomer of MATTPCA cannot be deemed novel, as a matter of law. However, as the district court recognized, that is not the correct view of the law of anticipation, which requires the specific description as well as enablement of the subject matter at issue. To anticipate, the reference "must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 [88 USPQ2d 1751] (Fed. Cir. 2008) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 [220 USPQ 193] (Fed. Cir. 1983)); see also, e.g., *In re Arkley*, 455 F.2d 586, 587 [172 USPQ 524] (CCPA 1972) ("[The] reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference" (emphasis in original)).

[1] The district court analyzed the question as whether a generic disclosure necessarily anticipates everything within the genus, and recognized that the answer depends on the factual aspects of the specific disclosure and the particular products at issue. See, e.g., *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 [78 USPQ2d 1417] (Fed. Cir. 2006) ("It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus."). In *In re Ruschig*, 343 F.2d 965, 974 [145 USPQ 274] (CCPA 1965), the court declined to find the disclosed genus anticipatory of everything within its scope, when the description of the genus would not lead a person of ordinary skill to a "small recognizable class with common properties." In this case the district court correctly declined to find that the references' general statements that these compounds consist of enantiomers constituted an anticipating disclosure of the separated dextrorotatory enantiomer of PCR 4099.

The district court discussed the cases on which Apotex particularly relied: *In re Petering*, 301 F.2d 676 [133 USPQ 275] (CCPA 1962), and *In re Schaumann*, 572 F.2d 312 [197 USPQ 5] (CCPA 1978). The court pointed out that in *Petering* and *Schaumann* the generic disclosure in the reference identified "specific preferences," which were met by the later-described species. We discern no clear error in the district court's finding that the references herein contained no such specific preferences. PCR 4099 is shown in the references as one of several compounds with desirable biological properties, but the district court did not clearly err in finding that the reference disclosure would not have led one of ordinary skill to recognize either an explicit or an inherent disclosure of its dextrorotatory enantiomer, as well as the bisulfate salt.

Apotex also relies on *In re Adamson*, 275 F.2d 952 [125 USPQ 233] (CCPA 1960),

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where the court held that although the reference did not state that the disclosed compound was a racemate, it would have been known to one of ordinary skill that synthetically produced chiral compounds are racemic. Sanofi does not dispute this statement of stereochemistry, but points out that knowledge of the existence of enantiomers is not a description of a specific enantiomer "substantially separated" from the other, as in claim 3 of the '265 patent. The district court cited *In re Imer*, 574 F.2d 1082 [197 USPQ 601] (CCPA 1978), which is explicit that "the novelty of an optical isomer is not negated by the prior art disclosure of its racemate." *Id.* at 1090. Also, *Adamson* and *May* were addressing rejections for obviousness, and neither case stated or suggested a previously unseparated and unknown enantiomer might be deemed anticipated by the known racemate.

The district court did not clearly err in finding that the statements in the '596 patent and its Canadian counterpart that the products therein consist of enantiomers are not a description of the specific dextrorotatory enantiomer clopidogrel or a suggestion of its unusual stereospecific properties. The knowledge that enantiomers may be separated is not "anticipation" of a specific enantiomer that has not been separated, identified, and characterized. The district court correctly held that neither the '596 patent nor its Canadian counterpart contains an anticipating disclosure of the subject matter of claim 3 of the '265 patent.

B

The parties also debated the question of enablement with respect to anticipation. The district court found that the asserted references are not enabling, for they contain no guidance as to how to separate the enantiomers of PCR 4099. Based on the evidence adduced at trial, the court concluded that absent such guidance, undue experimentation would be required.

Apotex argues that it is entitled to a presumption of enablement because the asserted references are patents, which are presumed to be enabling because they are presumed valid, citing *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 [65 USPQ2d 1385] (Fed. Cir. 2003) ("We hold that

an accused infringer should be similarly entitled to have the district court presume the enablement of unclaimed (and claimed) material in a prior art patent defendant asserts against a plaintiff.”). Apotex argues that the presumption should be particularly strong here, because the prior art patents belong to Sanofi. Thus Apotex argues that the general statements in the reference patents concerning enantiomers are presumptively enabling of the separate enantiomers of PCR 4099. Apotex states that it is irrelevant whether the separation of this specific enantiomer is shown in the references, because a person of ordinary skill in this field would know all of the existing techniques for separating stereoisomers, and would presumptively succeed in this particular separation. Apotex points out that the method that was eventually used by Sanofi was a well-known method, even if it involved some experimentation.

Any presumption of enablement of prior art does not exclude consideration of whether undue experimentation would be required to achieve enablement. See, e.g., *Elan Pharms*, 346 F.3d at 1054 (the reference must teach how to carry out the invention without undue experimentation). The factors relevant to whether experimentation is undue are discussed in, e.g., *In re Wands*, 858 F.2d 731, 737 [8 USPQ2d 1400] (Fed. Cir. 1988), and include the quantity of experimentation that was actually needed, the amount of guidance provided in the reference, the presence or absence of actual examples of the experimental procedure, the state of the knowledge already available concerning the subject matter at issue, and the predictability or unpredictability in the specific area of science or technology. The ‘596 patent reference states only that “if desired, its enantiomers are separated,” and similarly for the Canadian counterpart. The district court found that these references contain no description of how to separate the enantiomers of PCR 4099, and that “[d]iscovering which method and what combination of variables is required is sufficiently arduous and uncertain as to require undue experimentation, even by one skilled in the relevant art.” *Sanofi III*, 492 F.Supp.2d at 387. This finding has not been shown to be clearly erroneous. In *Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263 [84 USPQ2d 1099] (Fed. Cir. 2007), this court recognized the known difficulty of separating enantiomers and the unpredictability of their properties, and held that a reference that stated that a compound has enantiomers did not enable the separation of those enantiomers, where the reference did not teach how to obtain the enantiomer. *Id.* at 1268-69. We discern no clear error in the district court’s finding herein that the reference patents would not have enabled a person of ordinary skill to obtain

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clopidogrel substantially separated from the levorotatory enantiomer.

The district court’s ruling that claim 3 of the ‘265 patent is not invalid for anticipation is affirmed.

OBVIOUSNESS

The determination of obviousness is a matter of law based on findings of underlying fact, wherein the factors identified in *Graham v. John Deere Co.*, 383 U.S. 1 [148 USPQ 459] (1966), guide the inquiry:

Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

Id. at 17-18.

The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim. See *KSR Int’l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 [82 USPQ2d 1385] (2007); *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1448 [223 USPQ 603] (Fed. Cir. 1984). For chemical compounds, the structure of the compound and its properties are inseparable considerations in the obviousness determination. See *In re Sullivan*, 498 F.3d 1345, 1353 [84 USPQ2d 1034] (Fed. Cir. 2007); *In re Papesch*, 315 F.2d 381, 391 [137 USPQ 43] (CCPA 1963). Precedent establishes the analytical procedure whereby a close structural similarity between a new chemical compound and prior art compounds is generally deemed to create a prima facie case of obviousness, shifting to the patentee the burden of coming forward with evidence of nonobviousness. The evidence may take various forms, as relevant in the particular case. See, e.g., *Takeda Chem. Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1358, 1362-63 [83 USPQ2d 1169] (Fed. Cir. 2007) (prima facie case depends on whether the prior art provided a suggestion or reason to choose a specific lead

compound for modification, or to make the specific modification of the compound at issue); *Elsai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 [87 USPQ2d 1452] (Fed. Cir. 2008) (same). The ultimate determination is made in the context of the *Graham* factors, with the challenger having the ultimate burden of proving invalidity by clear and convincing evidence. See *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 [82 USPQ2d 1321] (Fed. Cir. 2007).

The district court assumed that Apotex had made a prima facie case of obviousness based on the reference patents' disclosure of the PCR 4099 racemate, the statements in the patents concerning enantiomers, and the general knowledge that enantiomers may be separated and may differ from each other in biological properties. Upon consideration of the *Graham* factors, the court held that the unpredictable and unusual properties of the dextrorotatory enantiomer and the therapeutic advantages thereby provided, weighed in favor of nonobviousness, and that Apotex had not met its burden of establishing otherwise.

Apotex argues that the recognition in the prior art that PCR 4099 is composed of enantiomers outweighs the effect of any unexpected or unpredictable properties of the separated dextrorotatory enantiomer. Apotex asserts that Sanofi's previous selection of PCR 4099 as a promising replacement for ticlopidine would have led a skilled artisan to start with PCR 4099 as a lead compound for further research. Apotex states that it was well known that enantiomers can have different levels of biological activity even if the exact allocation of properties is unpredictable, thereby rendering it obvious to separate the enantiomers and determine their properties. Apotex contends that the only features of clopidogrel bisulfate arguably not explicit in the prior art—the separation of the dextro- from the levorotatory enantiomer and its preparation as a bisulfate salt—required no more than well-known chemical techniques. Apotex cites known examples of other chiral compounds that exhibit stereoselectivity, and argues that the general knowledge that a favorable allocation of properties is possible suffices to render the separation obvious to a person of ordinary skill.

Apotex thus argues that there was motivation to separate the enantiomers of PCR 4099, and that a person of ordinary skill in the field would have been able to do so using known procedures, even if some experimentation was required, and then, upon separation of the enantiomers, routine testing would have revealed the favorable allocation of properties in the dextrorotatory isomer. Apotex asserts that it is not material that this allocation was unknown

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in advance and unpredictable, and that what matters is whether a person of ordinary skill would have had a reasonable probability of success in the separation and evaluation of the enantiomer, citing *Pfizer*, 480 F.3d at 1364, wherein this court observed that "case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success."

[2] Sanofi responds by challenging Apotex's view of the law, and citing the evidence on the factual premises of these arguments. At trial the expert witnesses for both sides agreed that a person of ordinary skill in this field in the mid-1980s would have known that enantiomers can exhibit different biological activities. However, the experts also agreed that it was not predictable whether such differences, if any, would be weak, moderate, or strong, or how they would be manifested. The experts agreed that no known scientific principle allows prediction of the degree to which stereoisomers will exhibit different levels of therapeutic activity and toxicity. The experts agreed that weak stereoselectivity of biological properties is more common than strong stereoselectivity, and that absolute stereoselectivity is rare. Sanofi witnesses testified as to the research team's belief, based on the earlier separations of two other thienopyridines, that separation of enantiomers was unlikely to be productive. Apotex's expert, when asked whether one could predict in advance the therapeutic and toxic properties of the enantiomers, stated: "No. I certainly don't believe you could predict that without separating them and trying it. I can't imagine anybody presuming anything else." The experts also agreed that activity and toxicity were more likely to be positively correlated, such that a reduction in toxicity would be expected also to reduce the beneficial activity. Witnesses also explained that it was known that for compounds whose biological activity is delivered through metabolism within the body, the acid environment in the stomach or other metabolic processes often restores the racemic state, thereby removing any potential benefit of a separated enantiomer. On the basis of this trial evidence, the district court found that a person of ordinary skill in this field would not reasonably have predicted that the dextrorotatory enantiomer would provide all of the antiplatelet activity and none of the adverse neurotoxicity. Clear error has not been shown in this finding, and in the conclusion of nonobviousness based thereon. See, *Papesch* 315 F.2d at 391 (a chemical compound and its properties are inseparable).

The district court also discussed the evidence concerning the process of separating the enantiomers of PCR 4099. Apotex argued that Sanofi's separation procedure was well known, and therefore that the separated components of the known racemate were obvious as a matter of law, whether or not they were deemed to have unexpected properties. The district court observed that in 1987 there were at least ten techniques that had been used to separate enantiomers, and that they all required experimentation to determine whether they could be successful for a particular compound, including choices of reagents, solvents, concentrations, temperature, and a variety of other conditions. The court observed that Pasteur's diastereomeric salt formation technique had long been described in chemistry textbooks, but that the textbooks also explain that the method is difficult and that there is no "infallible recipe" for obtaining separation.

The district court referred to the testimony of Sanofi's expert, Dr. Stephen G. Davies, who stated, in discussing the diastereomeric salt formation method, that it is difficult indeed to cause one enantiomer to crystallize out of solution while the other does not. As discussed *ante* in connection with anticipation, Mr. Badorc's eventual success came only after several failures using other known strategies for enantiomer separation. The court observed that although Sanofi had previously separated the enantiomers of two other thienopyridines, the diastereomeric salt formation method had succeeded in one case but failed in the other. The court also found that a person of ordinary skill would have recognized that it could be more difficult to separate the enantiomers of PCR 4099 than the two other compounds that Mr. Badorc had previously separated, because it would be understood by chemists that the methyl ester substituent in PCR 4099 could make it more susceptible to re-racemization, and thus resistant to successfully obtaining a separated product.

The district court found that this separation was not a simple or routine procedure and that success in separation, as well as the allocation of properties, was unpredictable. The court observed that Apotex did not cite any reference showing or suggesting any reliable method of separation for any analogous compounds. The court described the separation as a "paradigm of trial and error," *Sanofi III*, 492 F.Supp.2d at 370, and found that "neither the

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chemists at Sanofi nor a person of ordinary skill in the art could have reasonably expected that the separate enantiomers of PCR 4099 could be obtained at the time that Sanofi was contemplating whether to investigate them and, if obtained, they could not have predicted by what method and configuration." *Id.* at 371. The court found that Sanofi's expenditure of tens of millions of dollars for several years of development of the racemate PCR 4099, before separating the enantiomers, also weighed against finding that separation would have been obvious. Again, Apotex has demonstrated no clear error in the extensive finding of the district court concerning the difficulty and unpredictability of the separation of these enantiomers. These unchallenged findings undermine Apotex's argument in this appeal that the separation of the enantiomers would have been obvious. Only with hindsight knowledge that the dextrorotatory enantiomer has highly desirable properties, can Apotex argue that it would have been obvious to select this particular racemate and undertake its arduous separation. The application of hindsight is inappropriate where the prior art does not suggest that this enantiomer could reasonably be expected to manifest the properties and advantages that were found for this particular dextrorotatory isomer. See *Graham*, 383 U.S. at 36 (cautioning against hindsight whereby the teachings of the invention are read into the prior art); see also *KSR v. Teleflex*, 127 S. Ct. at 1742 (recognizing "hindsight bias" and "ex post reasoning" as inappropriate in determination of obviousness).

Concerning the bisulfate salt, the district court found no evidentiary support for Apotex's argument that the '596 patent taught the dextrorotatory enantiomer of PCR 4099 as the bisulfate salt. The PCR 4099 racemate is shown in the '596 patent as the hydrochloride, not the bisulfate. The district court observed that the scientific literature listed eighty acids as candidates for forming salts with basic drug compounds, fifty-three of which acids had been used in FDA-approved drugs. The experts of both parties agreed that whether a pharmaceutically suitable crystalline salt will form from a particular acid-base combination is unpredictable. The district court distinguished the facts of this case from those of *Pfizer* 480 F.3d 1348, where there was evidence that based on the prior art a person of ordinary skill would have narrowed the possible salts to only a few including the claimed besylate, whereas here Sanofi presented evidence that the prior art taught away from the use of sulfuric acid with an enantiomer, for strong acids could encourage re-racemization. Apotex has shown no clear error in the district court's finding, based on the trial evidence, that the facts distinguish this case from those in *Pfizer*.

Based on all of these findings, the district court concluded: "Whether or not it may have been 'obvious

to try' separating the enantiomers of PCR 4099 and, secondarily, preparing its dextrorotatory enantiomer as a bisulfate salt, the wide range of possible outcomes and the relative unlikelihood that the resulting compound would exhibit the maximal increase in antiplatelet aggregation activity and the absence of neurotoxicity makes clopidogrel bisulfate non-obvious." *Sanofi III*, 492 F.Supp.2d at 392. Apotex argues that the district court applied an incorrect inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general knowledge that enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 295 F.2d at 955, where the CCPA held that an enantiomer would have been obvious in view of its racemate. However, the scientific facts differed from these herein, for in *Adamson* the court found that it was "particularly expected" that the specific enantiomer would have the observed properties. In contrast, as *Sanofi* points out, in *In re May*, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant "established a substantial record of unpredictability vis-à-vis a highly significant combination of properties."

The determination of obviousness is dependent on the facts of each case. See *Graham*, 383 U.S. at 17-18. In *Forest Laboratories*, 501 F.3d at 1269, this court affirmed that the (+) enantiomer of citalopram would not have been obvious in light of the known racemate, when it was shown that the therapeutic properties of the (+) enantiomer were unexpected. In contrast, in *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.* 499 F.3d 1293, 1302 [84 USPQ2d 1197] (Fed. Cir. 2007), this court held that the ramipril isomer's potency was "precisely what one would expect, as compared to a mixture containing other, inert or near-inert stereoisomers." Apotex argues that *Aventis* is the closer analogy, but the evidence was directly contrary to that position. The district court entered extensive findings in this case on the unexpected and unpredictable properties of clopidogrel, and there was no

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contrary evidence suggesting, based on the prior art, that the stereoselective properties were "precisely what one would expect," as in *Aventis*.

Apotex also argued in the district court, and repeats on this appeal, that *Sanofi* separated the enantiomers only because of a possible future regulatory requirement concerning the separation of enantiomers. Apotex states that this future regulatory requirement would have alerted a person of ordinary skill to the need to separate isomers, and thus would have rendered it obvious to do so. The district court found that the sole evidence referring to this regulatory possibility, an internal *Sanofi* memorandum, was written several months after *Sanofi* had discontinued its development of the racemic PCR 4099 in favor of the dextrorotatory enantiomer; the court also cited the testimony and documentary evidence that *Sanofi* undertook this separation in order to study the adverse neurological effects of PCR 4099, and not because of a possible future regulatory requirement. *Sanofi* also points out, as the general knowledge in this field confirms, that the recognition that stereoisomers may exhibit different properties does not teach which results may ensue or how to separate any given enantiomers. We discern no error in the short shrift that the district court gave to this argument.

Apotex also argues that the district court did not take adequate account of the Supreme Court's holding in *KSR v. Teleflex* that the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." 127 S. Ct. at 1739. Apotex states that *Sanofi* did no more than separate the enantiomers and determine their properties, and that the properties were predictably those of the racemate, allocated between the enantiomers. *Sanofi* points out that this case does not concern a "combination of familiar elements" as in the *KSR* mechanical device made by combining known components to produce a combination having the properties of the known components. The evidence at trial well supported the finding that the result of this separation of enantiomers was unpredictable. We discern no error in the district court's implicit recognition that the principles of *KSR* do not affect the conclusion herein.

The district court thoroughly discussed the many issues and arguments raised by Apotex. We discern no error in the district court's findings that, on the state of the prior art, a person of ordinary skill would not have had the expectation that separating the enantiomers would be likely to produce an isomer having absolute stereoselectivity as to both the favorable antiplatelet activity and the unfavorable neurotoxicity. The totality of these findings, and the correct application of law, well support the district court's conclusion that invalidity had not been established by clear and convincing evidence.

AFFIRMED

- End of Case -

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